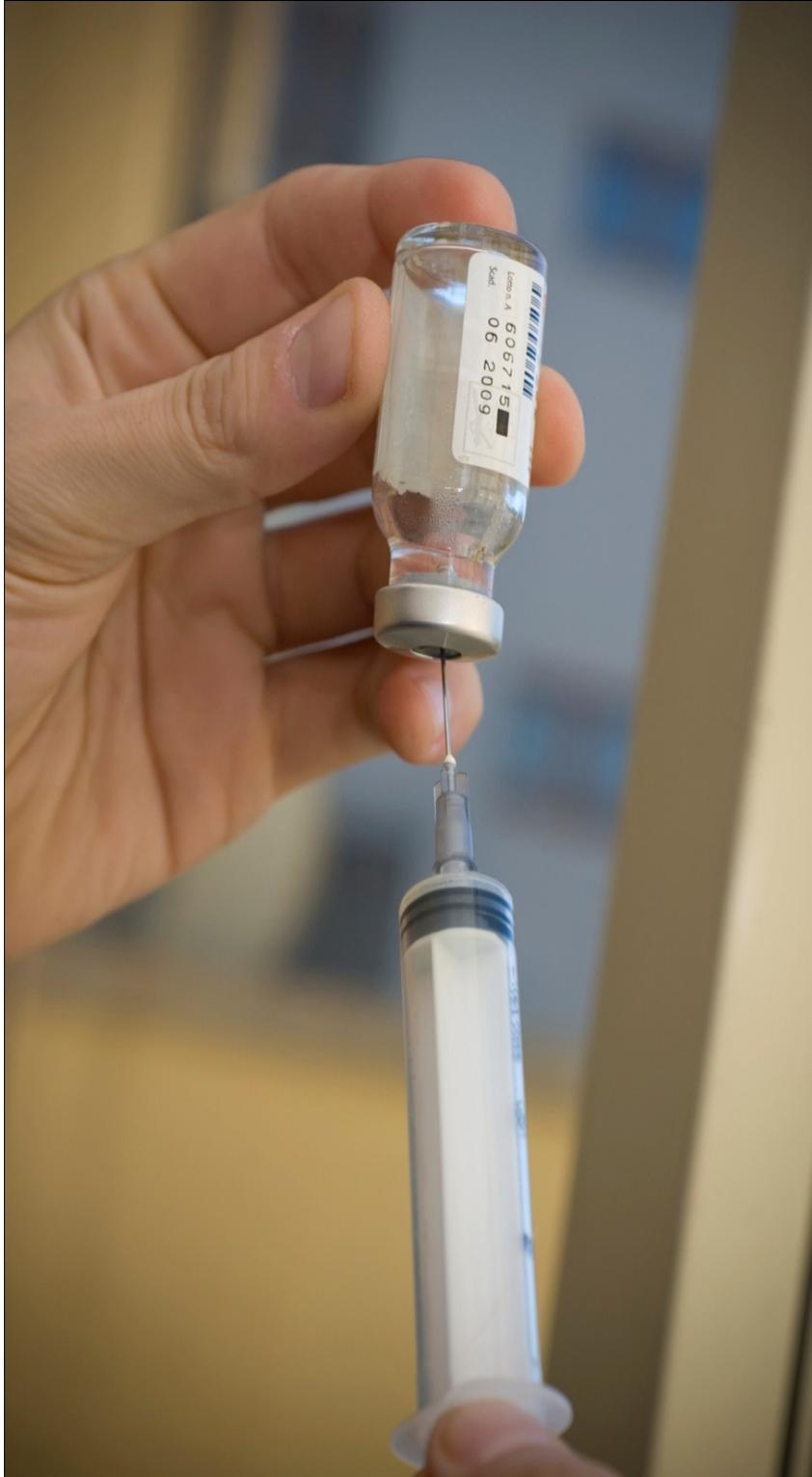


## Cancer Vaccine Therapies: Failures and Future Opportunities

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## EXECUTIVE SUMMARY

Since the early 1990s, cancer immunotherapy has provided hope to patients, physicians, and investors as a new treatment modality with limited side effects and superior efficacy. Cancer immunotherapy broadly includes passive immunization, active immunization, and immunostimulation<sup>1</sup>.

Passive immunotherapy is the transfer of an exogenous therapeutic agent to a patient where the therapy has a direct pharmacological action on the desired target. The best examples of passive immunotherapy are monoclonal antibodies (mAbs), which were hailed as “magic bullets” when they were developed in the 1970s.

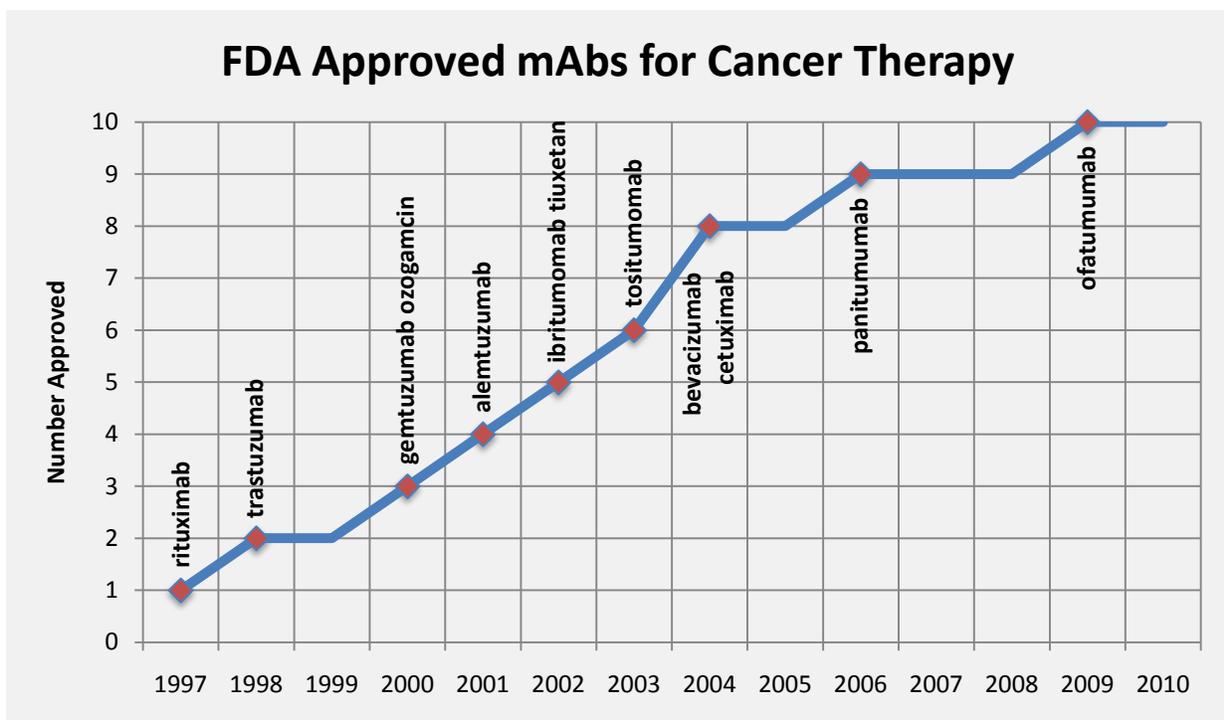
Clinical results with mAbs were largely disappointing for the first 10 years of development<sup>2</sup>. In fact, it wasn't until November 1997 that the first mAb for cancer therapy, Rituxan® (rituximab), was approved by the U.S. Food and Drug Administration (FDA). Developed by IDEC Pharmaceuticals, Rituxan® is a chimeric monoclonal antibody against the protein CD20 that is currently approved for the treatment of chronic lymphocytic leukemia (CLL), non-Hodgkin's Lymphoma (NHL), and rheumatoid arthritis (RA)<sup>3</sup>.

After reporting its first year of profitability in 1998, shares of IDEC Pharmaceuticals traded at a new all-time high of \$140 with a market capitalization above \$3.3 billion (see **Appendix D: Idec Pharmaceuticals - Anatomy of a Success**). Worldwide net sales of Rituxan® reached \$1.5 billion in 2002 and the following summer IDEC Pharmaceuticals acquired Biogen, Inc. in a stock transaction valued at approximately \$6.65 billion to create Biogen Idec, Inc. (BIIB)<sup>4</sup>.

While the success of Rituxan® spurred the development of other anti-CD20 mAbs, it wasn't until October 2009 that Arzerra® (ofatumumab) was approved by the FDA for the treatment of CLL. Arzerra®, which was developed by Genmab A/S (GNMSF.PK) and GlaxoSmithKline plc (GSK), is a human mAb that targets an epitope different from Rituxan® and other anti-CD20 mAbs<sup>5</sup>.

Today, passive immunotherapies represent one of the most successful therapeutic classes and there are currently ten mAbs approved for cancer therapy (see **Figure 1**: FDA Approval of cancer mAbs from 1997-2010). Three blockbuster products sold by the Roche Group (RHHBY) – Avastin® (bevacizumab), Rituxan®, and Herceptin® (trastuzumab) – collectively represented nearly US\$17 billion in revenue for 2009<sup>6</sup>. As useful as many of these mAbs have become in cancer therapy, they often have the greatest efficacy impact when used in combination with other therapeutic modalities, particularly cytotoxic agents<sup>7</sup>.

FIGURE 1: FDA APPROVAL OF CANCER MABS FROM 1997-2010



Similar to passive immunotherapy with mAbs, the early development of active immunotherapies has proven to be an enormous challenge<sup>8</sup>. In fact, we identified a dozen programs that failed in Phase III trials (see **Table 3**: Select Phase III Cancer Vaccine Trial Failures). Active immunotherapies are therapies that contain a specific antigen or set of antigens that are designed to activate the patient's own immune system to seek out and destroy cells that carry the same antigen. They have no direct therapeutic action, but rather rely on the patient's immune system to recognize and destroy the intended target.

While no active immunotherapeutics are currently approved for the treatment of cancer, the FDA has assigned a Prescription Drug User Fee Act (PDUFA) date of May 1, 2010, by which time it will respond to Dendreon Corporation's (DNDN) amended Biologics License Application (BLA) for Provenge® (sipuleucel-T). Dendreon is seeking licensure for Provenge® for men with metastatic castrate-resistant prostate cancer (CRPC). This event has reignited enthusiasm for the field of active immunotherapy and shares of Dendreon, which traded below \$5 in March 2009, recently hit all-time highs above \$40 and a market capitalization greater than \$5 billion.

As with any first-in-class product, regulatory delays are possible. For example, the BLA for Rituxan® was originally submitted on February 28, 1997, and the FDA requested additional data on certain aspects of the production process related to the bulk drug manufacture on August 29, 1997, which delayed approval until later that year (November 26, 1997). In view of the complexities of manufacturing and distributing an autologous cancer therapy, a similar request by FDA for Provenge® would not be unexpected and would likely occur around the PDUFA date using Rituxan®'s history as a guide.

If approved by the FDA, Provenge® would represent the first active immunotherapy for the treatment of cancer. However, unlike Rituxan®'s market monopoly that lasted for nearly 12-years, Provenge® could face competition in a relatively short period of time. Numerous active immunotherapies are in late-stage clinical development for prostate cancer – including a promising off-the-shelf vaccine set to begin a pivotal Phase III trial in 2010. In fact, nine product candidates are in clinical trials for the treatment of prostate cancer, representing the largest therapeutic area within the active immunotherapy market (see **Figure 8**: Active Cancer Immunotherapy Programs by Therapeutic Area and Development Stage).

Beyond Provenge®, there are a number of additional catalysts in 2010 that could ignite further interest in the field of cancer immunotherapy (see **Table 8**: Potential 2010 Catalysts for Cancer Vaccine Companies). Nearly 50 clinical programs involving active cancer immunotherapies are currently underway, including nearly a dozen that are in pivotal Phase III development with several BLAs planned in 2010 (see **Table 9**: Select Cancer Vaccine Companies and Programs).

For example, Bristol-Myers Squibb Company (BMY) has announced its intent to potentially file for regulatory approval for ipilimumab (with or without vaccine therapy) in metastatic melanoma in 2010 and has submitted Phase III data for presentation at the American Society for Clinical Oncology (ASCO) annual meeting held June 4-8, 2010. In addition, GlaxoSmithKline plc (GSK) is conducting the largest ever Phase III clinical trial in lung cancer treatment with its investigational MAGE-A3 ASCI immunotherapy, with the possibility for data presentation at ASCO 2010. Lastly, following the presentation of positive Phase III trial results at ASCO 2009, Biovest International, Inc. (BVTI.PK) expects to file a BLA for its BiovaxID® product candidate in NHL during 2010.

Accordingly, in this report we provide an overview of the cancer immunotherapy market and discuss some of the scientific, medical, clinical, and financial aspects of the major industry participants.

### **Objectives of the Report**

Some of the objectives of this research report are to:

- Provide an overview of the cancer immunotherapy market
- Identify disease indications currently being studied with cancer immunotherapy
- Identify the companies currently involved in cancer immunotherapy development
- Identify specific product candidates that offer the greatest market opportunities
- Assess the risks of cancer immunotherapy development and commercialization

### **Research Methodology**

MD Becker Partners adopted a three-fold approach for this study:

- Primary research focused on interviews with key opinion leaders involved in the field of cancer immunotherapy
- Secondary research focusing on utilizing information from peer-reviewed journal articles and reports on cancer immunotherapy
- Quantitative and qualitative analysis of the primary and secondary data using our industry experience and knowledge of the marketplace

## THE SCIENCE BEHIND CANCER VACCINES AND IMMUNOTHERAPY

The idea to stimulate one's own immune system to treat cancer dates back to 1891 when William Coley, Professor of Clinical Surgery at Cornell University, noticed the curative effect of an accidental bacterial infection in a patient with inoperable sarcoma<sup>9</sup>. As the scientific understanding of the immune system has significantly increased since Dr. Coley's time, scientists and physicians developed successful immune system related strategies to fight cancer, viral infection and autoimmune diseases. Today, mAbs are among the most successful modern immunotherapies and provide clinical benefit to a vast array of diseases unable to be treated with more conventional small molecule approaches.

### THE IMMUNE RESPONSE OVERVIEW

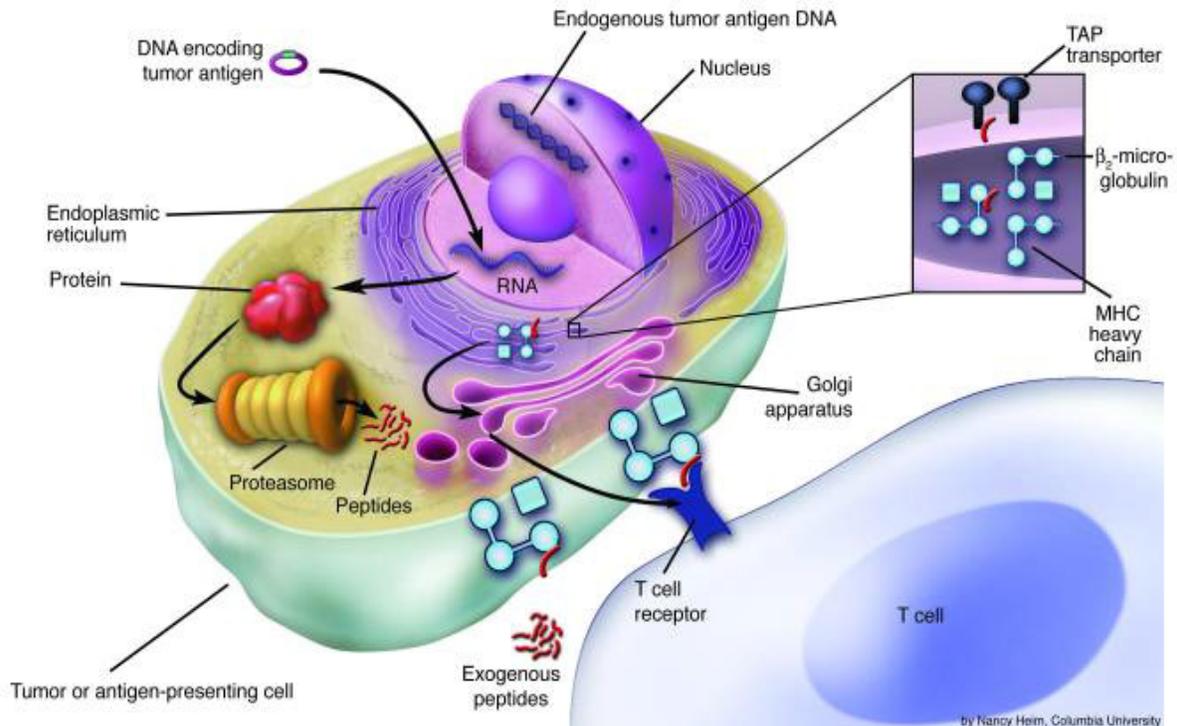
The immune system is a complex biological system designed to protect the host from pathogens and disease. Ideally, the immune system responds to external organisms or pathogens, while recognizing and avoiding the host cells. The human immune system is typically divided into two classes – innate and adaptive responses.

The innate immune system is the first line of defense against pathogens and most organisms have developed some form of innate immune response. When the skin or mucosa layer is broken, a complex biochemical and inflammatory signaling cascade consisting of lysozymes, complement, neutrophils, monocytes, macrophages, natural killer, and natural killer T-cells is initiated. The circulating cells ingest and degrade the invading pathogen.

The adaptive immune system is often called to action when the innate immune system is unable to cope with the invading pathogen. Antigen presenting cells (APCs), which include dendritic cells, macrophages, and B lymphocytes, recognize non-self antigens and present these antigens via the major histocompatibility complex (MHC) (see **Figure 2: Overview of Immune Response**). Exogenous antigens, such as those from a bacterial infection, are presented by MHC-II and recognized by CD4 T-cells. CD4 T-cells have no phagocytic activity but play an active role in activation of macrophages, cytotoxic T cells, and natural killer cells. Endogenous

antigens, such as viral infection or tumor cells, are displayed by MHC-I and recognized by CD8 T-cells. After clonal expansion, the CD8 T-cells seek out MHC-I presenting cells and induce cellular apoptosis.

FIGURE 2: OVERVIEW OF IMMUNE RESPONSE



The class I MHC antigen processing pathway acting as an internal surveillance mechanism to detect any abnormal or foreign protein synthesized in the cell. Tumor antigens encoded in the endogenous DNA of the tumor cell, or encoded in a DNA plasmid or viral vector vaccine taken up by an APC, are synthesized and cleaved by the 26S proteasome into fragments that are transported by TAP, the transporter associated with antigen processing, into the endoplasmic reticulum, where they are loaded onto newly synthesized class I MHC molecules that transport them to the cell surface for recognition by the T cell receptor. Source: *JOURNAL OF CLINICAL INVESTIGATION* by Jay A. Berzofsky, John C. Morris, Nancy Heim. Copyright 2004 by AMERICAN SOCIETY FOR CLINICAL INVESTIGATION. Reproduced with permission of AMERICAN SOCIETY FOR CLINICAL INVESTIGATION in the format Newsletter via Copyright Clearance Center.

An additional aspect of the adaptive response involves B cells and antibody production. When a mature B cell binds to a non-self antigen, the B cell internalizes the antigen and presents the antigen as an MHC/antigen complex. With the help of interleukins and T-cells, the B cells proliferate and differentiate into memory B cells and plasma cells. The plasma cells are responsible for producing antibodies, which have a very high affinity for antigens. Subsequent antigen stimulation results in a robust immune response and accelerated antigen elimination.

## SCIENTIFIC RATIONALE FOR IMMUNE SYSTEM MODULATION

Many cancers can be successfully treated with surgical removal of the cancerous tissue and delivery of various chemotherapeutic agents and radiation. For other cancers however, chemotherapeutics have severe side effects or have unfavorable pharmacokinetic profiles and thus prove only moderately effective. Some difficult to treat cancers may best be addressed by taking advantage of the evolutionarily developed immune system and modulating it to attack “foreign” tumor cells. Cancer immunologists believe that activation of the immune system against antigens found on tumor cells will initiate a body-wide search for tumor cells without the side effects of standard chemotherapy. Another key advantage is that if the cancer reappears, the immune system’s memory should be able to mount a rapid assault on the tumor. Finally, cancer vaccines have little interference with chemotherapeutic agents making them likely adjuvant treatments to traditional therapies.

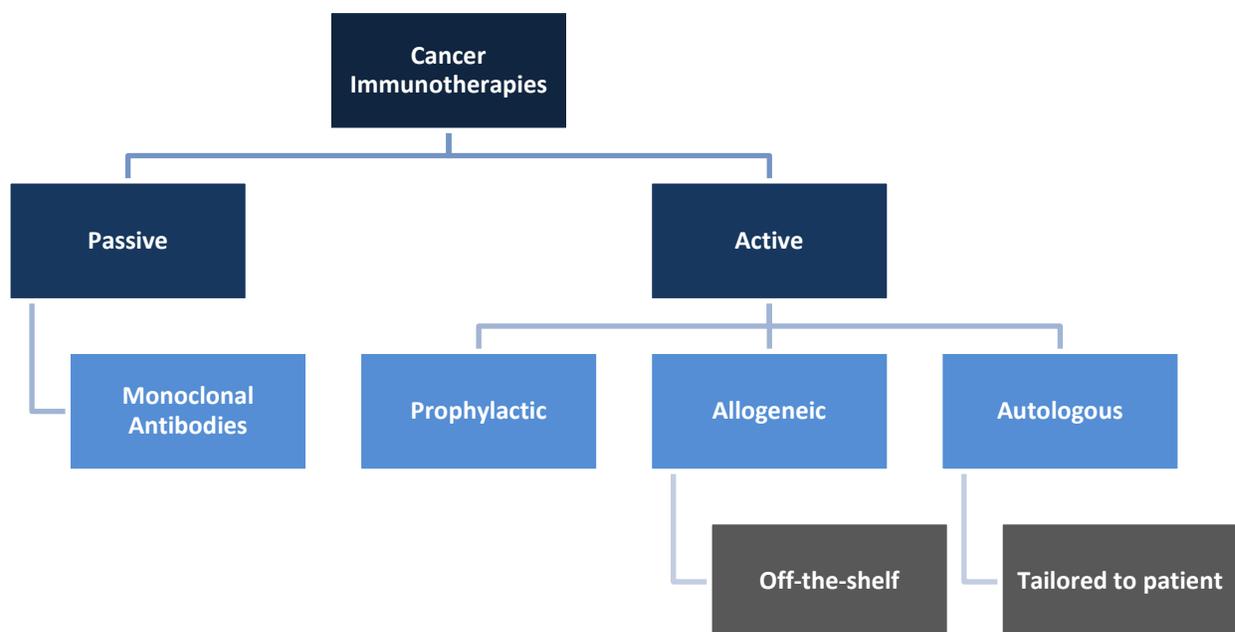
## CANCER VACCINES AND IMMUNOTHERAPY

Scientist's discovery of tumor-specific or tumor-associated antigens has led to several strategies around cancer vaccines and immunotherapy seen in the clinic today. Cancer vaccines are broadly divided into two main classes: passive and active therapies (see **Figure 3**: Cancer Immunotherapy categories).

Passive immunotherapy is the transfer of an exogenous therapeutic agent to a patient where the therapy has a direct pharmacological action on the desired target. The best example of a passive immunotherapy is a mAb directed against a tumor specific antigen, such as the HER-2/neu oncogenic protein in the case of Herceptin<sup>®10</sup>.

Conversely, active immunotherapies are therapies that contain a specific antigen or set of antigens that are designed to activate the patient's own immune system to seek out and destroy cells that carry the same antigen, such as the prostatic acid phosphatase (PAP) antigen in the case of Provenge<sup>®11</sup>. Active immunotherapies have no direct therapeutic action but rather rely on the patient's immune system to recognize and destroy the intended target.

FIGURE 3: CANCER IMMUNOTHERAPY CATEGORIES



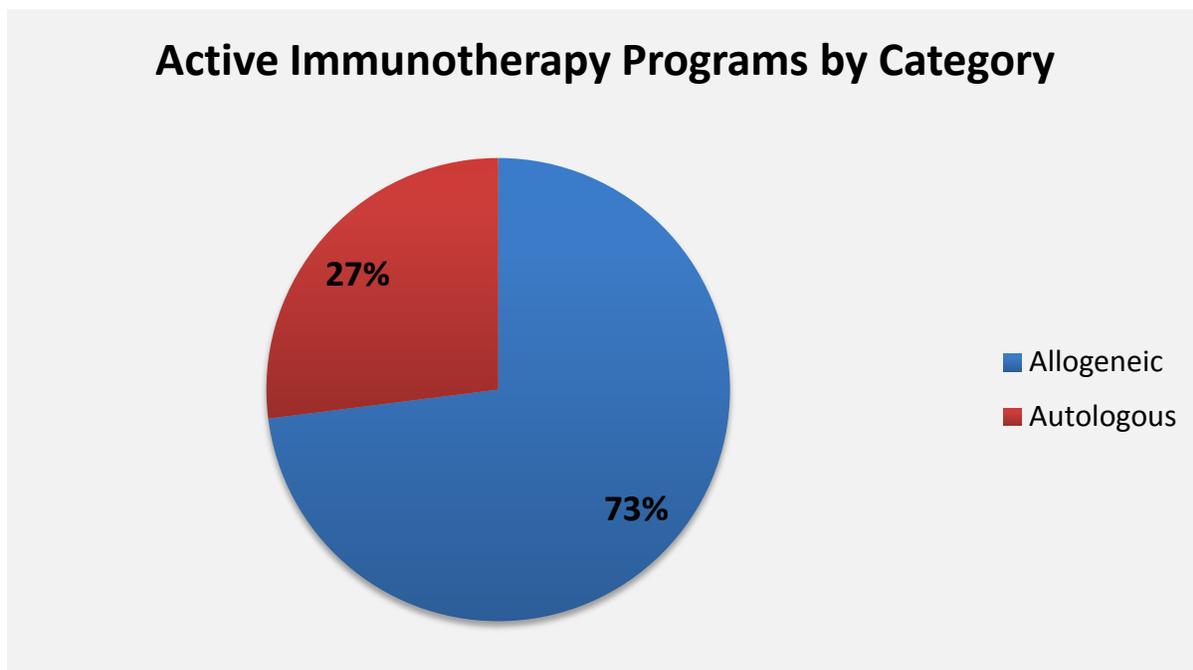
Active immunotherapies can further be broken down into three categories:

- **Prophylactic vaccines:** used to prevent a disease by introducing an antigen to a patient prior to the disease occurring. If a cancerous cell eventually arises and presents the antigen, the immune system will recognize that antigen as foreign and destroy the cell.
- **Allogeneic vaccines, or “off the shelf” vaccines:** active immunotherapies that contain a conserved antigen or groups of antigens across all patients.
- **Autologous vaccines, or “personalized” vaccines:** active immunotherapies that contain antigens derived from each individual patient.

Both allogeneic and autologous vaccines are reactionary and delivered to a patient after cancer diagnosis.

The majority of active cancer vaccines in the clinical development today are allogeneic (see **Figure 4: Active Immunotherapy Programs by Category**). This is likely due to the fact that allogeneic vaccines are less costly to manufacture, not as troublesome for the patient, and easier to distribute.

FIGURE 4: ACTIVE IMMUNOTHERAPY PROGRAMS BY CATEGORY



While both autologous and allogeneic vaccines have failed in pivotal trials (see **Table 3: Select Phase III Cancer Vaccine Trial Failures**), only Provenge<sup>®</sup>, an autologous therapy, has demonstrated a survival advantage in a Phase III study and is awaiting FDA approval.

There are several strategies that physicians and scientists are using to deliver both autologous and allogeneic vaccines to patients and they include cellular, peptide, gene transfer, and dendritic cells (see **Figure 5: Cancer Vaccine Programs by Strategy and Category**).

## PASSIVE IMMUNOTHERAPY AND ANTIBODIES

The first passive immunotherapy for cancer treatment took more than twenty years from discovery to reach commercialization. Similarly, it has been nearly twenty years from discovery to the commercialization of active immunotherapies for cancer treatment.

For example, in 1975, Drs. Köhler and Milstein published the first mAb technique<sup>12</sup>. More than twenty years later, Rituxan<sup>®</sup> became the first mAb approved for the treatment of cancer. Since the approval of Rituxan<sup>®</sup>, the FDA has approved mAbs for the treatment of other cancers, autoimmune diseases, organ transplants, and multiple sclerosis. In addition to improving the lives of patients, the approval of mAbs has proven profitable to many biotechnology companies and justified the investment required to develop and commercialize novel biologic therapies.

Similarly, the first complementary DNA (cDNA) expression cloning technique to identify tumor rejection antigens was discovered in 1991<sup>13</sup>. Nearly twenty years later, the first active immunotherapy, Provenge<sup>®</sup>, is widely expected to receive FDA approval for the treatment of cancer with several other cancer vaccines targeted for BLA filings in 2010.

While the role of mAbs in cancer treatment is well documented and not reviewed in this report, one investigational mAb is worth noting due to its potential synergy with active immunotherapy. Ipilimumab (also known as MDX-010, or MDX-101) is currently being studied with or without MDX-1379, a vaccine consisting of two gp100 melanoma peptides, in a Phase III trial. The peptides are recognized by cytotoxic T cells in melanoma patients that are positive for HLA-A2, representing approximately half of the population.

## BRISTOL-MYERS SQUIBB COMPANY (BMY)

Ipilimumab is a human monoclonal antibody that binds to cytotoxic T lymphocyte-associated antigen (CTLA)-4, a protein expressed on T-cells that is believed to play a critical role in regulating natural immune responses through the suppression of T cell activation and proliferation. The absence or presence of CTLA-4 on the cell surface can augment or suppress the immune system's T-cell response in fighting disease. Ipilimumab is designed to block the activity of CTLA-4, thereby sustaining an active T cell response in its attack on cancer cells<sup>14</sup>. Ipilimumab is currently being developed by Bristol-Myers Squibb and is undergoing late-stage clinical trials for the treatment of metastatic melanoma, lung cancer, and prostate cancer.

In an investment community presentation dated March 3, 2010, Brian Daniels, M.D., Senior Vice President, Global Development & Medical Affairs for Bristol-Myers Squibb, reviewed encouraging overall survival at one and two years in second-line metastatic melanoma from Phase II data previously presented at ASCO 2009, including an approximate doubling of survival at two years versus historical data. Upcoming milestones expected in 2010 include the presentation of Phase III data from a vaccine combination/monotherapy study in pretreated patients at ASCO 2010, data from first-line survival study in combination with dacarbazine (DTIC), and potential US and EU regulatory submissions<sup>15</sup>.

## PROPHYLACTIC ONCOLOGY VACCINES

The goal of a successful vaccine is to prepare the immune system for invasion of a foreign pathogen (e.g. virus, bacteria, or tumor) and prevent the disease from occurring as well as reduce the risk of transmission. Vaccines have been highly successful in the prevention of many historically debilitating diseases that are based on immune system recognition of pathogen-associated antigens<sup>16</sup>.

When a cancer-causing virus infects its target cell, the cell often expresses viral specific antigens. As a result of expressing non-self antigens, virus induced prophylactic treatments are the natural first anti-cancer target therapy. Ninety percent of pathogen induced cancers are attributed to four infectious agents: hepatitis B virus (HBV), hepatitis C virus (HCV), human

papilloma virus (HPV), and Helicobacter pylori<sup>17</sup>. The FDA approved vaccines for HBV and HPV, while vaccines are not yet available for HCV and H. pylori.

### MERCK & CO., INC. (MRK)

In June 2006, Merck's Gardasil<sup>®</sup> was approved by the FDA as a vaccine against HPV. The vaccine protects against infection from four strains of HPV<sup>18</sup>. In girls and young women ages 9 to 26, Gardasil<sup>®</sup> helps protect against two types of HPV that cause about 75% of cervical cancer cases, and two more types that cause 90% of genital wart cases. Gardasil<sup>®</sup> also helps protect girls and young women ages 9 to 26 against 70% of vaginal cancer cases and up to 50% of vulvar cancer cases. On October 16, 2009 the FDA approved Gardasil<sup>®</sup> for use in boys and men, 9 through 26 years of age, for the prevention of genital warts caused by HPV types 6 and 11, making Gardasil<sup>®</sup> the only HPV vaccine approved for use in males and females. Worldwide sales of Gardasil<sup>®</sup> in 2009 were \$1.1 billion, a 20 percent decrease compared with the prior year<sup>19</sup>.

### GLAXOSMITHKLINE PLC (GSK)

GlaxoSmithKline's Cervarix<sup>®</sup> is the second HPV vaccine to reach the market. On October 16, 2009, the FDA approved Cervarix<sup>®</sup> (human papillomavirus bivalent, types 16 and 18, vaccine, recombinant) for the prevention of cervical pre-cancers and cervical cancer associated with HPV types 16 and 18 for use in girls and young women (aged 10-25). Sales of Cervarix<sup>®</sup> reached £187 million in 2009<sup>20</sup>.

Most cancers are the result of oncogene mutations resulting in the transformation of a normal cell into an immortalized cancer cell. Because chemically or genetically induced tumor cells are derived from normal cells, researchers have not developed prophylactic vaccines for these cancers and other therapeutic approaches are required.

## AUTOLOGOUS AND ALLOGENEIC CANCER IMMUNOTHERAPIES

Researchers and clinicians agree that there is no clear advantage of either autologous or allogeneic therapies and multiple delivery strategies for each category have been developed

(see **Figure 6: Types of Vaccine Delivery**). Both possess strengths and weaknesses versus the other type. Autologous vaccines appear to have an advantage over allogeneic vaccines with regards to efficacy, but also have potential problems with regard to commercial viability. Autologous vaccines are often more expensive due to the personalized medicine approach, less effective if the tumor rapidly mutates, and may be difficult to manufacture depending on the amount of starting material (tumor cells). The advantages and disadvantages of the various strategies are listed in **Table 1: Advantages and Disadvantages of Cancer Vaccine Strategies**, Modified from Berzofsky.

**FIGURE 5: CANCER VACCINE PROGRAMS BY STRATEGY AND CATEGORY**

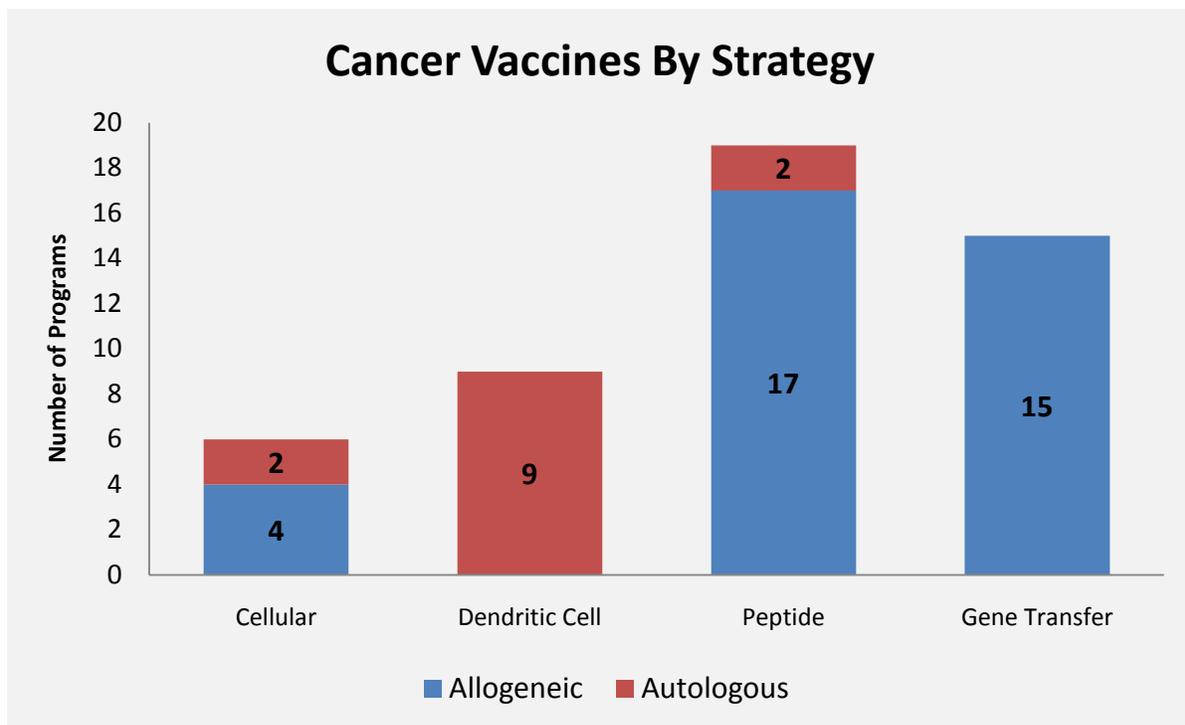
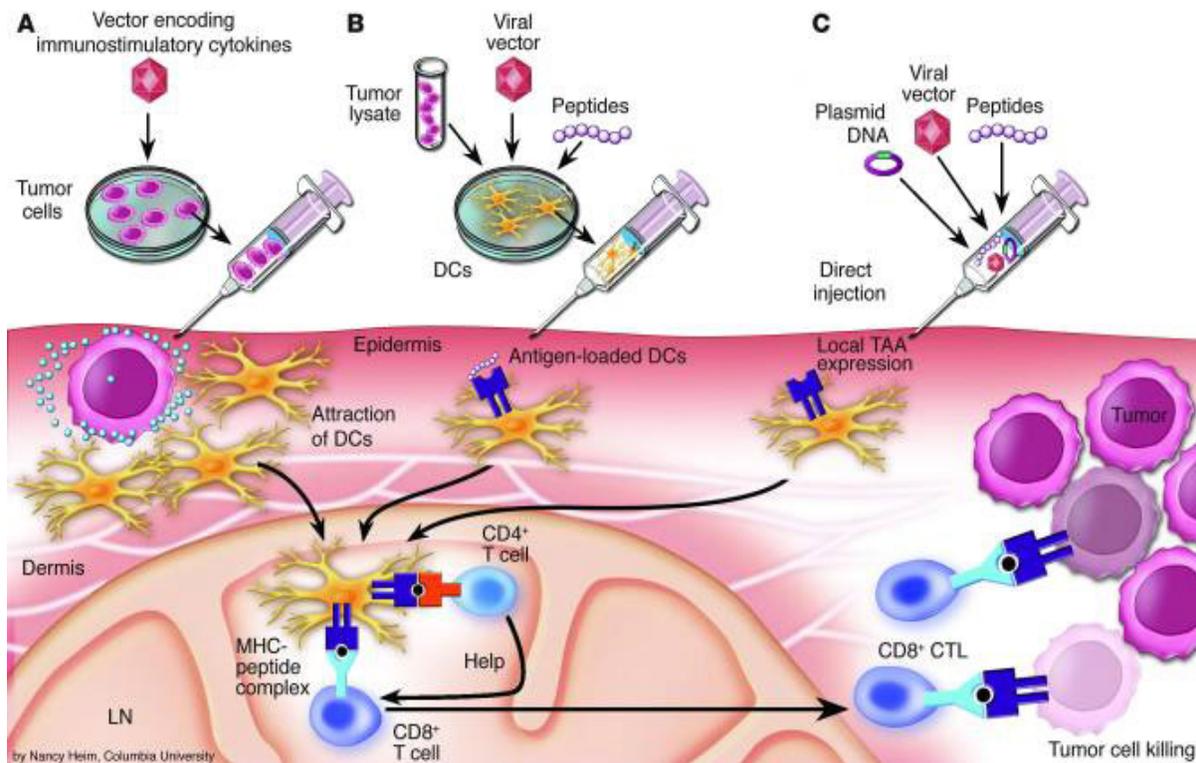


FIGURE 6: TYPES OF VACCINE DELIVERY



Approaches to antitumor vaccination. (A) Irradiated tumor cells transduced with a viral gene transfer vector encoding a cytokine such as GM-CSF attract APCs (DCs) that acquire, process, and present tumor-associated antigens (TAAs) encoded by the vector in the context of MHC. (B) DCs can be directly loaded by incubation with tumor protein lysates or peptides with sequences based on expressed tumor antigens, or by viral gene transfer vectors expressing TAAs. (C) TAAs can be locally supplied to DCs by the direct injection of peptides, viral gene expression vectors, or naked DNA expression plasmids. DCs migrate to secondary lymphoid tissues where they present the antigen epitopes to T cells to generate an antitumor cytolytic T cell response. Source: *JOURNAL OF CLINICAL INVESTIGATION* by Jay A. Berzofsky, John C. Morris, Nancy Heim. Copyright 2004 by AMERICAN SOCIETY FOR CLINICAL INVESTIGATION. Reproduced with permission of AMERICAN SOCIETY FOR CLINICAL INVESTIGATION in the format Newsletter via Copyright Clearance Center.

TABLE 1: ADVANTAGES AND DISADVANTAGES OF CANCER VACCINE STRATEGIES, MODIFIED FROM BERZOFSKY<sup>21</sup>

Strategy	Category	Advantages	Disadvantages	Examples
Cellular	Allogeneic	<ul style="list-style-type: none"> <li>Controlled/ well studied cell lines</li> <li>Manipulated to overexpress many antigens</li> <li>Administered with adjuvants or modified to express adjuvants</li> </ul>	<ul style="list-style-type: none"> <li>Not all antigens may be present that are needed to activate a full immune response</li> <li>Stable cell line required</li> <li>Weak antigen presentation by many cell lines</li> <li>Poor ability to mount full immune response</li> </ul>	BioSante: GVAX NovaRx: Lucanix VaxOnco: Onyvax-P
	Autologous	<ul style="list-style-type: none"> <li>Likely to express relevant antigens; antigens do not need to be predefined</li> <li>Most direct cancer immunotherapy</li> <li>Administered with adjuvants or modified to express adjuvants</li> </ul>	<ul style="list-style-type: none"> <li>Cell lines must be isolated, cultured/manipulated, and grown to a patient specific quantity</li> <li>Weak antigen presentation by many cell lines</li> <li>Difficulty/ costs manufacturing</li> </ul>	Advaxis: ADXS11-001 Avax: MVAX/ LVAX/ OVAX MolMed: M3TK Vaccinogen: OncoVax
Dendritic cell	Allogeneic	<ul style="list-style-type: none"> <li>Powerful use of APC</li> <li>Able to generate large numbers of cells</li> <li>Multiple antigen loading techniques</li> <li>Skips the APC recognition step needed by cellular technique</li> </ul>	<ul style="list-style-type: none"> <li>Requires knowledge of the antigens needed to activate the immune response</li> <li>Weak antigen presentation by tumor cells may result in low immune response</li> <li>Possibility of toleration</li> </ul>	n/a
	Autologous	<ul style="list-style-type: none"> <li>Patient specific antigens</li> <li>Powerful use of APC</li> <li>Generate large numbers of cells</li> <li>Multiple antigen loading techniques</li> <li>Skips the APC recognition step needed by cellular technique</li> </ul>	<ul style="list-style-type: none"> <li>Weak antigen presentation by tumor cells may result in low immune response</li> <li>Possibility of toleration</li> <li>Manufacturing and costs</li> </ul>	Argos: AGS-003 Geron: GRNVAC1 ImmunoCellular: ICT-107 Northwest Biotherap: DCVax Prima Biomed: CVac Quantum Immunologic: OFA Dendreon: sip/lapuleucel
Peptide	Allogeneic	<ul style="list-style-type: none"> <li>Antigens can be mutation specific</li> <li>Easily manufactured</li> <li>Easily combined with other peptides or therapies</li> </ul>	<ul style="list-style-type: none"> <li>Requires knowledge of the specific epitope</li> <li>Limited immunogenicity</li> <li>Requires adjuvant</li> <li>Weak antigen presentation by tumor cells may result in low immune response</li> </ul>	Aphera: NeuVax Bristol-Myers: MDX-1379 Cel-Sci: Multikine CellDex/Pfizer: CDX-110 Generex Biotech: AE37 GlaxoSmithKline: MAGE-3 Immatics: IMA901 /IMA910 Immutep: IMP321 Oncothyreon: Stimuvax
	Autologous	<ul style="list-style-type: none"> <li>Peptides are cancer mutation specific</li> <li>Easily combined with other peptides or therapies</li> </ul>	<ul style="list-style-type: none"> <li>Difficult to determine if all of the necessary peptides needed to mount a full response are isolated</li> <li>Requires knowledge of the specific epitope</li> <li>Limited immunogenicity</li> <li>Requires adjuvant</li> <li>Large amount of starting tumor is needed for manufacturing</li> <li>Weak antigen presentation by tumor cells may result in low immune response</li> </ul>	Antigenics: Oncophage BioVest Int'l: BioVaxID Genitope Corp: MyVax
Gene Transfer	Allogeneic	<ul style="list-style-type: none"> <li>Express relevant tumor antigens</li> <li>Easy to produce/ manufacture</li> <li>Easy co-expression of adjuvants</li> </ul>	<ul style="list-style-type: none"> <li>Toxicity and immune reaction to virus</li> <li>Requires knowledge of the specific epitope</li> <li>Weak antigen presentation by tumor cells may result in low immune response</li> </ul>	Alphavax: PMSA/CEA Bavarian Nordic: PROSTVAC Cytos Biotech: CYT004 Inovio: VGX3100/V930,34 MannKind: MKC1106-PP Oxford Biomed: TroVax Progenics: PSMA VRP Transgene: TG4010 Vical: Allovectin-7

## CELLULAR VACCINES

Cellular vaccines can be either autologous or allogeneic. One of the primary advantages of cellular vaccines is that cells could induce an immune response to antigens that are not currently known. For example, a particular cancer needs to express a group of antigens in order to elicit an effective immune response, all of which may not be known to the physician. If the patient is delivered, through peptide infusion or gene transfer, a defined set of antigens, there is the risk that the patient may not activate the necessary immune response (i.e. not all of the antigens required were introduced). Further, cell based vaccines might be able to target a wider population of tumor cells despite the adaptability of tumor cells within a particular cancer patient<sup>22</sup>.

### BIO SANTE PHARMACEUTICALS, INC. (BPAX)

BioSante is developing its GVAX cancer vaccines, which the company acquired through a merger with Cell Genesys in 2009. GVAX immunotherapy is comprised of cancer cell lines that are genetically modified to secrete granulocyte-macrophage colony stimulating factor (GM-CSF), an immunostimulatory cytokine, and then irradiated for safety. GVAX immunotherapy is designed to be administered through intradermal injections on an outpatient basis. GVAX has been studied in Phase III trials in prostate cancer and is currently the subject of Phase II trials in acute myeloid leukemia (AML) and pancreatic cancer.

BioSante recently announced positive results and receipt of Orphan Drug designation from the FDA for GVAX in the treatment of AML. In a paper published in the peer-reviewed journal *Blood*, clinical investigators reported on the results of a Phase II study of GVAX accompanied by immunotherapy-primed lymphocytes after autologous stem cell transplantation in hematologic malignancies. Fifty-four subjects were enrolled, with 28 (52%) receiving a pre-transplantation GVAX AML dose. A total of 46 (85%) subjects achieved complete remission during the treatment period. For all patients who achieved complete remission, the 3-year relapse-free survival (RFS) rate was 47.4% compared to 61.8% in the GVAX-treated group. While the overall survival rate in all subjects was 57.4%, it was 73.4% in the GVAX-treated group.

In addition, BioSante recently received Orphan Drug designation for GVAX in the treatment of pancreatic cancer. Currently, GVAX is being studied in a Phase II clinical trial in pancreatic cancer designed to determine the safety, overall survival and response to GVAX combined with various anti-cancer agents, as compared to those agents alone or in combination with other agents.

Two Phase III studies with GVAX were previously conducted by Cell Genesys in prostate cancer:

VITAL-1 was a Phase III clinical trial designed to compare GVAX cancer immunotherapy as a monotherapy to Taxotere® (docetaxel) chemotherapy plus prednisone in castrate-resistant prostate cancer (CRPC) patients with metastatic disease who were asymptomatic with respect to cancer-related pain. The primary endpoint of the trial was an improvement in survival. In 2007, the VITAL-1 trial completed enrollment with 626 patients at 131 sites in North America and the European Union. On August 27, 2008, Cell Genesys announced that it had requested the study's Independent Data Monitoring Committee (IDMC) to conduct a previously unplanned futility analysis of VITAL-1. Based on the results of that analysis, Cell Genesys terminated the VITAL-1 trial in October 2008.

VITAL-2 was a Phase III trial designed to compare GVAX immunotherapy in combination with Taxotere® to Taxotere® plus prednisone in CRPC patients with metastatic disease who were symptomatic with respect to cancer-related pain. The primary endpoint of the trial was also improvement in survival. VITAL-2 was initiated in June 2005 and had enrolled 408 patients at 115 clinical trial sites located in North America and the European Union prior to study termination. On August 27, 2008, Cell Genesys announced its decision to terminate enrollment and treatment with GVAX immunotherapy in VITAL-2 as recommended by its IDMC due to an imbalance in deaths between the two treatment arms of the VITAL-2 study.

In part, clinical investigators blame the failure of VITAL-1 and VITAL-2 on the advanced nature of the disease in the patients studied. For example, in a subgroup analysis based on work done at the National Cancer Institute (NCI), patients that had a predicted survival of at least 18 months did better on the GVAX arms than those patients in the control arms. Interestingly, investigators are looking at the overall survival follow-up from VITAL-1 due to the fact that only

60% of the deaths (371 deaths / 621 enrolled) were reported at the time of the non-prespecified futility analysis. Investigators are hoping that the study will become positive due to the late effect seen with cancer vaccines, although additional studies would likely be required for registration.

## DENDRITIC CELLS

Dendritic cells (DC) are antigen-presenting cells that play a key role in both the innate and adaptive immune response<sup>23</sup>. After activation, DCs migrate to the lymphoid organs from the peripheral tissues and activate a potent T cell response as well as mediate overall immune system communication. Many tumors target endogenous DCs using tumor associated suppressive factors resulting in impaired function of the DCs.

DCs have been used as an immunotherapy since the 1990s, although to date, clinical response has rarely exceeded 15%. First and second generations of DCs provided a suboptimal immunogenic response, but provided a proof-of-principle that therapeutic immunity can be elicited<sup>24</sup>. The most recent third generation of DCs includes “non-exhausted” mature DCs in combination with cytokines. Although several companies are developing third generation DC based immunotherapies, they differ in their delivery, co-factors, genetic manipulation of the cells and ultimately clinical response.

## DENDREON CORPORATION (DNDN)

Dendreon has the most advanced active immunotherapy program. The company recently completed a second Phase III study of Provenge® in CRPC and is seeking approval for the first active immunotherapy on the market.

Provenge® is an active immunotherapy product candidate consisting of autologous peripheral blood mononuclear cells, including antigen presenting cells, which are cultured *ex vivo* with a recombinant fusion antigen consisting of prostatic acid phosphatase (PAP) and GM-CSF. PAP is primarily expressed on prostate tumors reducing the risk of cross tissue immune reactions. GM-CSF is a cytokine that facilitates production of white blood cells and augments DC migration.

After the *ex vivo* processing, a patient receives a total of three, hour-long infusions – one every two weeks.

Provenge® is a clinically experienced compound with a well-defined safety and efficacy profile. In a Phase I/II trial published in 2000, Dendreon demonstrated a significant antigen specific T cell and B cell response, which correlated to its preclinical models<sup>25</sup>. Based on these results, Dendreon initiated a Phase III trial, which did not meet its primary endpoint, time to disease progression ( $p=0.052$ ) despite demonstrating a 4.5 month improvement in survival<sup>26</sup>. Even with a positive recommendation from the FDA's Office of Cellular, Tissue and Gene Therapies Advisory Committee regarding the fact that Provenge® was reasonably safe (vote 17-0) and that there was substantial evidence of the product's efficacy (vote 13-4), in May 2007 the FDA requested additional clinical data in support of the efficacy claim contained in the BLA.

On April 14, 2009 Dendreon announced the results of its second Phase III trial for Provenge®. The trial for men with advanced prostate cancer, met its primary endpoint of improving overall survival compared to a placebo control. The 512-patient, multi-center, randomized, double-blind, placebo-controlled IMPACT (**IM**muno**th**erapy for **P**rostate **A**deno**C**arcinoma **T**reatment) study enrolled men with metastatic androgen-independent prostate cancer was conducted under a Special Protocol Assessment (SPA) agreement with the FDA. In addition to proving safety, Dendreon demonstrated the following statistically significant endpoints:

- Provenge® extended median survival by 4.1 months compared to placebo (25.8 months versus 21.7 months);
- Provenge® improved 3-year survival by 38% compared to placebo (31.7% versus 23.0%);
- The IMPACT study achieved a p-value of 0.032, successfully exceeding the pre-specified level of statistical significance defined by the study's design (p-value less than 0.043); and
- Provenge® reduced the risk of death by 22.5% compared to placebo (HR=0.775).

Dendreon also completed a Phase I trial of lapuleucel-T (APC8024) in patients with HER-2/neu-expressing tumors. Lapuleucel-T is an investigational active immunotherapy product consisting of autologous peripheral blood mononuclear cells, including antigen presenting cells, which are cultured *ex vivo* with BA7072, a recombinant fusion antigen consisting of portions of the intracellular and extracellular regions of HER-2/neu linked to GM-CSF. In the Phase I trial,

eighteen patients were enrolled and treated with patients demonstrating an immune response to the immunizing antigen (BA7072) at week 8 compared with week 0 as measured by T lymphocyte proliferation and IFN-gamma enzyme-linked immunospot assay. The majority (94.7%) of adverse events associated with treatment were grade 1 or 2. Two patients experienced stable disease lasting more than 48 weeks<sup>27</sup>.

## PEPTIDE VACCINES

Peptide vaccines are based on tumor-associated antigens delivered directly to a patient in order to elicit an adaptive immune response and can be either allogeneic or autologous. The choice of antigen(s) includes differentiation antigens that are expressed by tumors derived from one particular tissue, shared antigens that are specifically expressed in tumors of different types but not in normal tissues, antigens that are expressed at low level in normal tissues and over-expressed in tumors of different types, and tumor-specific post-translational modified proteins<sup>28</sup> (see **Table 2**: Select Antigen Targets for Cancer Vaccines). The peptides can be delivered directly or through a carrier system such as bacterial cells, lipid mixtures, or virus particles.

One antigen target for peptide vaccines is the spontaneously occurring deletional mutant of the human epidermal growth factor receptor (EGFR) known as EGFRvIII, which is commonly expressed in glioblastoma multiforme (GBM)<sup>29</sup>. Another example is melanoma antigenic epitope 3 (MAGE-3), which is expressed in many tumors of several types, such as melanoma, head and neck squamous cell carcinoma, lung carcinoma and breast carcinoma, but not in normal tissues except for testes<sup>30</sup>.

Due to the fact that mutations on cancer cells can lead to unique tumor specific antigens that have yet to be identified, autologous peptide vaccines may have a clinical advantage. However, allogeneic peptide vaccines may possess certain commercial advantages, such as mass-production, storage, and distribution to a wide number of patients. The primary limitation of allogeneic peptide vaccines is that the predefined antigen may only be applicable to a select group of cancer patients or those patients that present a particular HLA type. In order to be

truly effective at treating tumors, vaccination regimens should generate large T-cell responses; the clinical efficacy of these therapies remains mixed depending on the level of T-cell response.

TABLE 2: SELECT ANTIGEN TARGETS FOR CANCER VACCINES

Antigen	Company
<b>Shared tumor-specific</b>	
MAGE-3	GlaxoSmithKline, ImmunoCellular, MolMed
NY-ESO-1	GlaxosmithKline
<b>Differentiation</b>	
CEA	Alphavax
gp-100	ImmunoCellular, Bristol-Myers Squibb
MART-1	Cytos Biotechnology
TRP-2	ImmunoCellular
<b>Overexpressed in cancer</b>	
HER-2/neu	Apthera, Bavarian Nordic, Dendreon, Genex Biotech, Immunocellular
MUC-1	Oncothyreon, Prima Biomed, Transgene SA
PRAME	Mannkind
PSMA	Alphavax, MannKind, Progenics
<b>Mutated</b>	
EGFRvIII	CellDex Therapeutics/Pfizer

### CELLEX THERAPEUTICS, INC. (CLDX)

Under a collaboration announced in April 2008, Celldex Therapeutics and Pfizer, Inc. (PFE) are developing CDX-110, a peptide vaccine targeting EGFRvIII, which is highly expressed in glioblastoma cells. CDX-110 utilizes an EGFRvIII-specific 14-amino acid peptide, PEP-3, which is chemically conjugated to keyhole limpet hemocyanin (KLH) and has been used for the generation of EGFRvIII-specific antibodies induction of cellular immune responses, and as a derivation of targeted toxins<sup>31</sup>.

Unlike EGFR, EGFRvIII is only found on cancerous cells and is a well-validated target for cancer therapy due to its cancer specificity and role as an oncogene. EGFR is over expressed in

approximately 50–60% of GBM tumors and EGFRvIII is expressed in 24–67% of cases<sup>32</sup>. When an agonist binds to a wild-type EGFR, the receptor forms a homo or hetero-dimer and initiates a tyrosine kinase signaling cascade resulting in cell proliferation. The EGFRvIII mutation (deletion of AA 6-274) does not bind to its agonist but leads to continuous EGFR signaling and uncontrolled cell division because it is constitutively autophosphorylated<sup>33</sup>.

Traditional chemotherapy has proven to be ineffective in treating GBM. As a result of its ineffectiveness, conventional therapy for a malignant brain tumor represents the most expensive medical therapy per quality-adjusted life-year saved currently provided in the United States<sup>34</sup>.

There are a number of challenges in developing immunotherapy approaches to treat GBM. First, the brain has historically been regarded as immunologically privileged organ site, as evidenced in part by the fact that vaccines that work outside the central nervous system have proven ineffective within the brain<sup>35</sup>. Second is the well-documented impairment of T and B cell immunity in these patients,<sup>36, 37</sup> although there is evidence that CD8+ and CD4+ cells are able to penetrate the blood brain barrier<sup>38</sup>.

On May 30, 2009, Celldex Therapeutics and Pfizer announced the presentation of updated data from two clinical trials of CDX-110 in newly diagnosed GBM at ASCO<sup>39</sup>:

In the ACTIVATE single arm Phase II study, 18 patients with newly diagnosed and optimally resected EGFRvIII-positive GBM received CDX-110 as a monotherapy following completion of chemoradiation with concurrent temozolomide. Median overall survival (OS) was 26 months and median time to progression (TTP) was 14.2 months. Additionally, three patients remained without relapse more than 4 years from surgery and continued to receive the vaccine within the clinical trial.

In the ACT II single arm Phase II study, 22 patients with newly diagnosed and optimally resected EGFRvIII-positive GBM received CDX-110 in combination with maintenance temozolomide after having completed chemoradiation with concurrent temozolomide. Median time to progression TTP was 15.2 months and three patients continued without relapse after more than two years.

Results to date from this ongoing study estimate median overall survival to be 23.6 months (data are not yet final). In addition, and in line with preclinical data that suggested the combination with temozolomide could augment immune responses, patients show robust serological evidence of an immune response against EGFRvIII.

Efficacy data from both ACTIVATE and ACT II compare favorably to data for a historical control group of 17 patients, matched for EGFRvIII expression, extent of resection and performance status (Median TTP: 6.3 months; Median OS: 15.0 months). In both studies, CDX-110 was generally well tolerated with local injection site reactions being the most commonly reported toxicity. ACT III, a multicenter, single-arm Phase II clinical trial in GBM in which all patients will receive CDX-110 in combination with maintenance temozolomide, is ongoing.

### GLAXOSMITHKLINE PLC (GSK)

Another allogeneic peptide vaccine in development targets melanoma antigenic epitope 3 (MAGE-3), which is often overexpressed by 1000X in tumor cells versus normal cells<sup>40</sup>.

GlaxoSmithKline is developing investigational MAGE-A3 Antigen-Specific Cancer Immunotherapeutic (ASCI) as a targeted immunotherapy treatment for metastatic melanoma and non-small cell lung cancer (NSCLC). ASCI is packaged in liposomes to enhance delivery and combined with a proprietary adjuvant mix to induce a robust T cell response. The AS15 adjuvant mix includes monophosphoryl lipid A (MPA), QS-21 (by Antigenics, Inc.) and CpG oligonucleotide<sup>41</sup>.

Phase II data that GlaxoSmithKline reported at ASCO in 2007 demonstrated a 27% reduction in the relative risk of NSCLC recurrence following surgery in patients treated with MAGE-A3 ASCI, compared to placebo. In the patient population selected for the presence of the predictive gene signature, a 43% reduction in the relative risk of relapse was observed. GlaxoSmithKline initiated a Phase III safety and efficacy trial in MAGE-A3-positive NSCLC patients (stage IB, II and IIIA) who have undergone complete surgical resection (MAGRIT; MAGE-A3 Adjuvant Non-Small Cell Lung Cancer Immunotherapy). MAGE-A3 ASCI is being evaluated as adjuvant therapy in

about 2,270 MAGE-A3-positive patients with completely resected stage IB, II or IIIA NSCLC in the large MAGRIT trial. The primary endpoint for the MAGRIT trial is disease free progression.

### ANTIGENICS, INC. (AGEN)

Antigenics is a clinical stage biotechnology company developing an autologous peptide vaccine called Oncophage® (vitespen; formerly HSPPC-96). Oncophage® is a personalized extract of heat-shock protein (HSP) peptides derived from the patient's tumor that has been tested in nearly 800 patients in clinical trials throughout North America and Europe<sup>42</sup>. HSPs are a group of proteins that are expressed in response to cellular stress and facilitate protein folding. In addition, some HSPs play a role in the presentation of antigens on the cell surface to the immune system. The Oncophage® technology is based on scientific founder Dr. Pramod Srivastava's discovery that APCs have receptors for HSPs. Oncophage® captures the unique HSP antigens presented on tumor cells and when injected back into the patient, activate the immune system to attack tumor cells containing the HSP antigens.

One of the potential concerns surrounding Oncophage® (and other autologous peptide vaccines) is the size of tumor needed to generate sufficient peptides to mount a large enough immune response. In order to manufacture Oncophage®, the patient's tumor is surgically removed and shipped to the Antigenics' manufacturing facility in Massachusetts. The required HSPs are purified, filtered, and shipped back to the patient for injection.

In this regard, due to the relatively high manufacturing failure rate of Oncophage® in a Phase III metastatic melanoma study, the company indicated that the trial would not qualify for registration. Analysis of the Phase III data showed that patients with less advanced disease who received at least 10 doses of Oncophage® had improved median survival of approximately 18.4 months versus patients who received physician's choice of treatment (31.2 months vs. 12.8 months, respectively; hazard ratio = 0.45; two-sided P value= 0.03)<sup>43</sup>.

In March 2006, Antigenics announced disappointing top-line results from its Phase III study of Oncophage® in more than 700 patients with renal cell carcinoma (RCC), which was triggered based on the number of events reported by study investigators. However, an independent

review by the trial's Clinical Events Committee (CEC) revealed that a substantially smaller number of events had actually occurred. The CEC also reported that 17% of the patients had detectable disease at baseline and should not have been randomized into the study, and that 42% of the reported recurrences and deaths had occurred in these patients, thereby reducing the power to detect a true difference<sup>44</sup>. While a subgroup analyses for "intermediate stage" RCC patients treated with Oncophage<sup>®</sup> showed a significant increased survival benefit ( $p=0.026$ ), these results would need to be confirmed in a prospective trial.

On April 8, 2008, the Russian Ministry of Public Health approved Oncophage<sup>®</sup> for use in Russia in the treatment of kidney cancer patients at intermediate risk for disease recurrence. However, on October 21, 2009, Antigenics announced that the Committee for Medicinal Products for Human Use (CHMP), of the European Medicines Agency (EMA), informed the company at an oral meeting to anticipate a negative opinion on the marketing authorization application (MAA) for Oncophage<sup>®</sup> in early-stage, localized renal cell carcinoma. Following the announcement, shares of Antigenics fell 62% from \$2.08 to approximately \$0.80.

In October 2009, updated data from a Phase I/II clinical trial of Oncophage<sup>®</sup> for recurrent high grade glioma was presented at a medical conference. Data reported in the first 20 patients treated with Oncophage<sup>®</sup> show a median survival of 10.1 months. While survival data continues to accrue on all patients in the study, to date six patients (30 percent) have survived at or beyond 12 months. These early data are comparable with the recently reported median survival of 9.2 months with Avastin<sup>®</sup> in patients with recurrent high-grade glioma<sup>45</sup>. To date, side effects observed in this study have been minor and have included injection-site reaction, fatigue, and headaches.

The Phase I/II single-arm trial is designed to enroll about 50 patients with recurrent high- grade glioma to evaluate median overall survival, progression-free survival and immunologic response to vaccine treatment. Patients undergo surgery to remove their tumors, which are then used to manufacture their patient-specific vaccines. Patients receive four weekly doses of Oncophage<sup>®</sup> and then bi-weekly doses thereafter in the absence of disease progression, unacceptable toxicity, or vaccine depletion.

An additional Phase II study is underway evaluating Oncophage® in combination with Temodar® (temozolomide) in newly diagnosed glioma patients.

## GENE TRANSFER

Gene transfer, with respect to tumor vaccines, is the introduction of exogenous DNA, either through virus or plasmid based delivery, into the tumor cells where the tumor cells would overexpress the desired antigen. This approach allows the tumor cells to act as antigen presenting cells and presents the tumor cells as target for T cells. A commonly expressed tumor antigen, such as PSA or CEA, delivered in combination with adjuvants is the most common form of cancer immunotherapy gene transfer.

### VICAL, INC. (VICL)

Vical currently has one of the most advanced gene transfer cancer immunotherapy programs. Vical's Allovectin-7® is a plasmid/lipid complex containing the DNA sequences encoding HLA-B7 and  $\beta 2$  microglobulin, which together form a major histocompatibility complex, or MHC, class I. Allovectin-7® is injected directly into tumor lesions and is believed to produce an immune response against the lesion and distant metastatic sites through several mechanisms.

In January 2010, Vical announced the company completed enrollment of the planned 375 patients in its pivotal Phase III trial (AIMM) of Allovectin-7® in patients with metastatic melanoma. The primary endpoint of the study, which is being conducted under a SPA with the FDA, is a comparison of overall response rates at 24 weeks or more after randomization. The study will also evaluate safety and tolerability as well as survival. While enrollment was complete in January 2010, Vical doesn't expect that trial results will be available in 2010.

### TRANSGENE SA

In March 2010, Transgene announced the signing of an exclusive option agreement with Novartis (NVS) for the development and commercialization of its TG4010 product candidate for the treatment of NSCLC and other potential indications. Transgene is eligible to receive up to a total of approximately €700 million.

TG4010 (MVA-MUC1-IL2) uses the Modified Vaccinia Ankara (MVA) virus vector, a highly attenuated poxvirus strain that has been tested extensively in humans as a smallpox vaccine and is known to strongly stimulate innate and adaptive immune responses to antigens. TG4010 expresses the entire MUC1 gene sequence and has the potential to generate an immune response to all antigenic epitopes of MUC1 along with the sequence coding for the cytokine Interleukin 2 (IL2) to help stimulate specific T-cell response.

In a previously completed Phase IIb study in NSCLC, Transgene retrospectively identified that patients with normal levels of activated natural killer cells survived significantly longer in the experimental arm than in the control arm. Transgene expects to initiate a pivotal, global Phase IIb/III clinical trial with TG4010 in NSCLC by the end of 2010. This study will involve approximately 1,000 patients with MUC1-positive NSCLC who have normal levels of activated natural killer cells at time of trial entry.

Results from the phase IIb portion of this trial are expected to be available in the first quarter of 2012 and Novartis will have up to 90 days after receiving results from Transgene for this phase IIb portion to exercise its option. The final results are expected to become available by the end of 2013.

## CLINICAL TRIAL DIFFICULTIES

Through 2007, it is estimated that more than 6,000 cancer patients have participated in late-stage clinical studies of active cancer immunotherapies<sup>46</sup>. However, both the medical and financial communities are aware of the vast number of late-stage cancer vaccine clinical failures. We identified a dozen programs that failed in Phase III trials (see **Table 3: Select Cancer Vaccine Phase III Trial Failures**). While the trials have cost tremendous amounts of time and capital, there are valuable lessons that can be learned from these failures.

### TOO EARLY FOR THE CLINIC

Many experts in the medical community believe that companies sent their cancer vaccine products into the clinic prior to having enough understanding about how their product works on the molecular level. There are two primary reasons for rushing the product into the clinic. The first is when the first cancer vaccines were being developed, the preclinical models were not sophisticated enough to predict clinical outcomes, such as those able to predict immune tolerance to tumor cells and initiation of autoimmune diseases. The second reason is financial. Many companies thought that the safety and limited efficacy of early trials represented sufficient data to proceed to large-scale trials. There was a race to market coupled with a desire to keep R&D costs low. The combination of these reasons turned out to be disastrous for several companies.

For example, Therion Biologics Corporation opted to develop its PANVAC vaccine in pancreatic cancer due to the short life expectancy associated with the disease, which translates into shorter clinical trials. The company went from a Phase I trial directly into a multicenter Phase III trial that ultimately did not meet its primary efficacy endpoint of demonstrating longer overall survival compared with palliative chemotherapy or best supportive care. This result demonstrated the risks of testing agents of this class in high tumor burden, fast progressing, second line settings. While the trial failed in Phase III development and resulted in Therion filing for bankruptcy in 2006, the underlying technology was promising and has demonstrated encouraging results in prostate cancer (see PROSTVAC).

TABLE 3: SELECT PHASE III CANCER VACCINE TRIAL FAILURES

Company	Product	Description	Indication(s)	Results
<b>IDM Pharma, Inc.</b>	mifamurtide (L-MTP-PE)	Immune activator containing liposomal MTP-PE	Osteosarcoma	Did not enhance event-free survival
<b>Therion Biologics</b>	PANVAC	Allogeneic, poxvirus expressing MUC-1 and CEA	Pancreatic cancer	No improvement in overall survival
<b>Biomira, Merck KGaA</b>	Theratope	Allogeneic, MUC-1 epitope linked to KLH delivered by an adjuvant liposome complex	Breast cancer	No improvement in time to disease progression or overall survival
<b>Cell Genesis</b>	GVAX	Allogeneic, whole cell tumor vaccine that is engineered to secrete GM-CSF	Prostate cancer	No improvement in overall survival
<b>CancerVax</b>	Canvaxin	Allogeneic, whole-cell plus BCG	Melanoma	No improvement in overall survival
<b>Progenics, Bristol-Myers</b>	GMK vaccine	Allogeneic, GM <sub>2</sub> ganglioside coupled with KLH and formulated with QS-21	Melanoma	No improvement in relapse-free or overall survival
<b>Corixa</b>	Melacine	Allogeneic melanoma lysates plus Detox	Melanoma	No improvement in relapse-free or overall survival
<b>Antigenics</b>	Oncophage	Autologous, peptides (HSP)	Melanoma, Renal cell	No improvement in overall survival
<b>Favrille</b>	Specifid (mitumprotimut)	Autologous, administered with KLH and GM-CSF	Follicular lymphoma	No improvement in time to progression
<b>Genitope Corp</b>	MyVax, GTOX-99	Autologous, whole tumor cell approach with GM-CSF/KLH	Follicular non-Hodgkin's lymphoma	No improvement in progression-free survival
<b>Cellcor, Cytogen</b>	ALT	Autologous, lymphocyte therapy	Renal cell carcinoma	No improvement in overall survival

## WEAK IMMUNE RESPONSE AND IMMUNOSUPPRESSION

Historically, one of the primary reasons for cancer vaccine failures is that the vaccine elicited an immune response that was too weak to fight off the tumor cells. T cells are activated in concert with a number of co-stimulatory molecules (CD80, CD86), ligands (CD40L, CD28), and negative feedback molecules (CTLA-4). Many of the current cancer vaccine clinical trials introduce their vaccine in combination with immune stimulating agents, regulators and cytokines such as GM-CSF, keyhole limpet hemocyanin (KLH), IL-2, IL15, cyclophosphamide, and TGF- $\beta$ <sup>47</sup>. GM-CSF, of the most commonly used stimulatory factors, is an FDA approved product that enhances dendritic cell migration to regional nodes<sup>48</sup>. Early on, pharmaceutical companies were reluctant to use stimulatory agents because they did not show efficacy as a monotherapy; however, the lack of immune response has created a need to find the optimal adjuvant products. The importance of preclinical dosing and scheduling in combination with these stimulatory factors is essential for maximizing clinical efficacy.

Tumor progression is a game of cat and mouse between the host (and therapies) and the tumor. In an ovarian cancer study by Zhang et al. the 5-year overall survival rate was 38.0% among patients whose tumors contained T cells and 4.5% among patients whose tumors contained no T cells in the islets ( $p < .001$ )<sup>49, 50</sup>. Advanced tumors have evolved to create a microenvironment that prevents the endogenous immune system from fighting off the tumor. Regulatory T cells regulate the activation of T cells and inhibit their function by producing TGF- $\beta$ <sup>51</sup>. Within a tumor microenvironment, regulatory T cells accumulate and directly suppress anti-tumor T cell actions. In addition to regulatory T cells, myeloid-derived suppressor cells (MDSCs) inhibit effector T cells via multiple mechanisms. One of the best examples of controlling tumor-induced immunosuppression is through the CTLA-4 antibody although some patients responded with autoimmune induced toxicity.

A successful vaccine therapy must take into account the tumor microenvironment. If the therapy is able to show a robust T cell response, the immune therapy will still be ineffective if 1) the T cells cannot reach the tumor, or 2) the T cells are inactivated at the site of the tumor. Many leading immune oncologists believe that finding the right combination (vaccine plus

chemotherapy, vaccine plus radiation therapy, vaccine plus immune stimulating agent, etc.) is one of the keys to developing a successful vaccine therapy.

## CLINICAL TRIAL DESIGN AND ENDPOINTS

The execution of well-defined clinical trials is critical to FDA approval and the clinical adoption of a paradigm shifting technology or therapy. It is essential to understand the challenges facing cancer vaccine therapies, such as trial design, clinical endpoints, and general physician opinions in order to anticipate the next wave of cancer vaccine approvals and their future impact within the medical community.

For example, Response Criteria In Solid Tumors (RECIST) is a set of rules that determine a cancer patient's clinical response. RECIST measures tumor shrinkage as the primary evaluation criteria for new therapeutic modalities. Many oncologists believe that combining RECIST criteria with a patient's response may be more effective in measuring a new treatment than RECIST alone. This has been especially evident in the evaluation of signal transduction inhibitors, where several agents have demonstrated prolonged stable disease without corresponding reductions in tumor size.

In this regard, one of the best examples is a Phase III trial for renal cell carcinoma patients receiving Nexavar® (sorafenib), a tyrosine protein kinase inhibitor targeting the Raf/Mek/Erk pathway. In a Phase III trial, patients receiving Nexavar® demonstrated a doubling of progression-free survival while partial response (PR) rates and complete response (CR) rates using RECIST were 10% or lower (10% PR, <1% CR)<sup>52</sup>. Global Nexavar® net sales reported by Onyx Pharmaceuticals, Inc. (ONXX) were \$843 million for the full year 2009<sup>53</sup>.

Similar to targeted therapy with small molecule signal transduction inhibitors, vaccine therapy may represent a new way of treating cancer that requires rethinking how we evaluate clinical efficacy. Cancer vaccines have minimal side effects compared to other chemotherapies and although they may not drastically reduce tumor size, they may offer an improvement in progression free survival.

When it comes to evaluating active cancer immunotherapies, it is important to distinguish between bad clinical trial design or execution and failed product candidates. For instance, it is clear from previous trials, such as GVAX in prostate cancer, that there is an inverse relation between a patient's ability to elicit a robust immune response and the number of prior therapies. In addition, the premature evaluation of clinical trial results can be dangerous, as was the case with GVAX and Antigenics' phase III RCC trial with Oncophage®.

Within trial design, dosing and scheduling are a subset of errors often ignored in the development of active cancer immunotherapies. Administration of a cancer vaccine is unique among most pharmacological modifiers because the vaccine does not have a direct effect on its target cell but rather initiates an exponential biological response. This response creates a dynamic relationship between the vaccine, the immune system, and the tumor. Several trials demonstrated a clinical response to immune therapy only after patients received the vaccine followed by chemotherapy<sup>54, 55</sup>.

Upon review of past pivotal trial failures, it has becoming evident that future cancer vaccine clinical development should take the following into consideration:

- **Proper patient profile identification:** Not all vaccines will work for each patient, similar to how some kinase inhibitors are only effective in specific oncogene derived cancers. There is considerable underlying heterogeneity in some of the cancers and patient cohorts selected for study which can mask what may be efficacy for certain subgroups of patients.
- **Proper early stage dosing/scheduling trial:** The dose and schedule of a successful vaccine should not be given based on the amount of "drug" that is manufactured. Instead, a successful program will determine the most effective dosing and scheduling early on in clinical development.
- **Low tumor burden, limited previous therapies:** The most effective long-term therapies will be in those patients with a low tumor burden. The vaccine must be able to reach the tumor and be active at the tumor site in order to mount a

successful immune response. In addition, the more previous therapies the patient has been exposed to, the less chance of success.

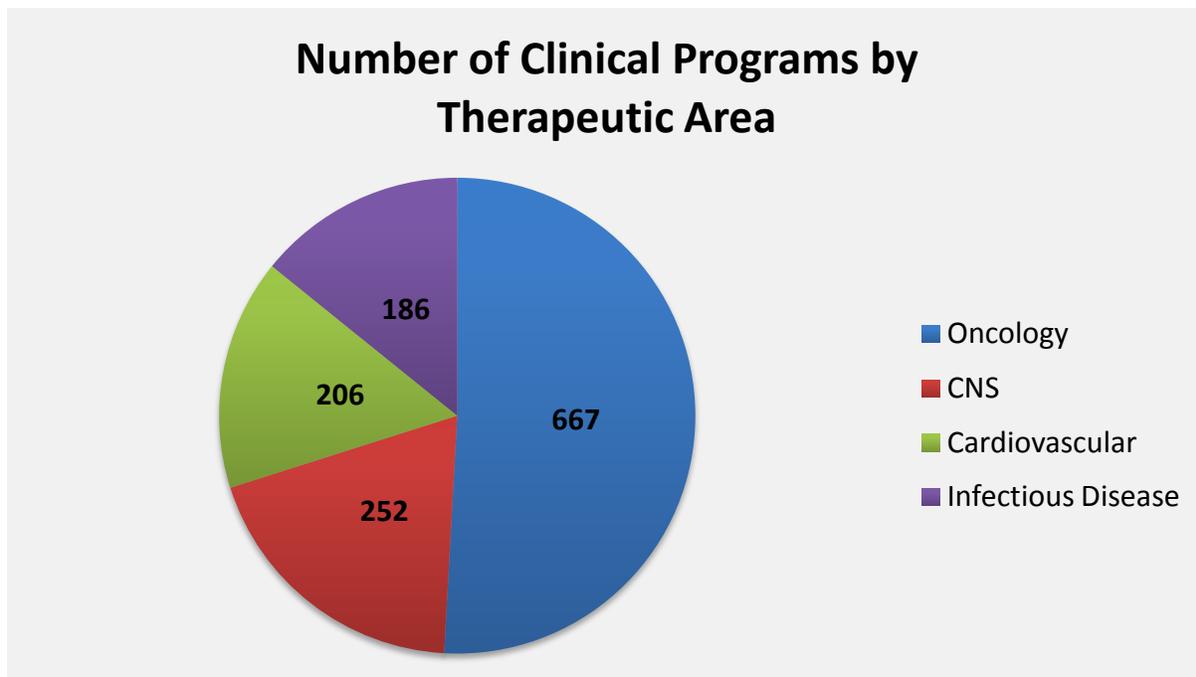
- **Enough survival time to administer multiple doses:** The most effective vaccines will not show significant tumor reduction but will rather preserve progression free survival with minimal side effects.
- **Combination therapy:** In order to achieve a low tumor burden, the vaccine must be given in combination with chemotherapy or the patient must have received at least one round of chemotherapy.

## THE MARKET

### THE CANCER MARKET

The market size of cancer patients is one of the fastest growing therapeutic areas and is expected to grow over the next several years. As the population continues to age and grow, the incidence of cancer is also expected to rise. Fortunately, the five-year survival rate is 66%, up from 50% in 1975 due to new therapies and earlier diagnosis<sup>56</sup>.

FIGURE 7: CLINICAL PROGRAMS BY THERAPEUTIC AREA



Despite the improved outcomes since 1975, patients and physicians are demanding new and improved cancer therapies. New cancer medicines make up approximately 51% of the major clinical programs (Oncology, CNS, Cardiovascular, Infectious Disease) currently in development (see **Figure 7: Clinical Programs by Therapeutic Area**)<sup>57</sup>. In 2009, 1 out of every 5 new approvals by the Center for Drug Evaluation and Research (CDER) was in the oncology space<sup>58</sup>. The number of FDA approved drugs combined with the number of new drugs in development makes cancer therapy product development a very crowded space.

## COMMERCIALIZATION CHALLENGES

In many ways, the commercialization challenges facing developers of cancer vaccines are similar to other biologic agents. However, because there are no approved active vaccine therapies, undoubtedly there are unknown roadblocks that lie ahead. The three greatest commercialization challenges facing vaccine companies include: 1) Good manufacturing practice (GMP), 2) cost/benefit analysis by patient and payer, and 3) physician acceptance/integration into medical practice.

GMP manufacturing of cell lines may present problems in the short term for vaccine companies. Allogeneic cell lines and peptides are much more straightforward compared to autologous approaches. cGMP manufacturing control and compliance issues for allogeneic cells include the exposure to cells and animal products. These issues are always a concern for biologics but are nothing new to the industry. Autologous cells on the other hand may face a more difficult cGMP process. The issues include the necessity to manufacture a pre-determined amount of product based on an individual surgical procedure, manufacturing cells based on a single cell line, and production of a “consistent” product from unique cell isolations. Both allogeneic and autologous production must ensure that the final product expresses the desired antigen under desired cell culture conditions. Together, the cGMP challenges facing cancer vaccine companies are difficult yet surmountable. Because of the personalized medicine approach, especially with autologous cells, manufacturing costs may be a greater challenge than the process itself.

The manufacturing challenge for companies who are developing whole cell vaccines is to demonstrate batch-to-batch consistency for the vaccine used in clinical studies and to show that comparable vaccine batches have the same capacity to achieve an acceptable level of biological activity that may be related to efficacy. The details of an acceptable biological potency assay will have to be worked out on a case-to-case basis since each product will be unique in terms of cell characterization, antigen expression and dose response. In order to obtain FDA approval, the whole cell vaccine has to meet the agency’s potency requirements. If Provenge® is approved by the FDA, it will be the first autologous whole cell cancer vaccine to

meet the FDA's chemistry, manufacturing and control (CMC) requirements, including the potency assay.

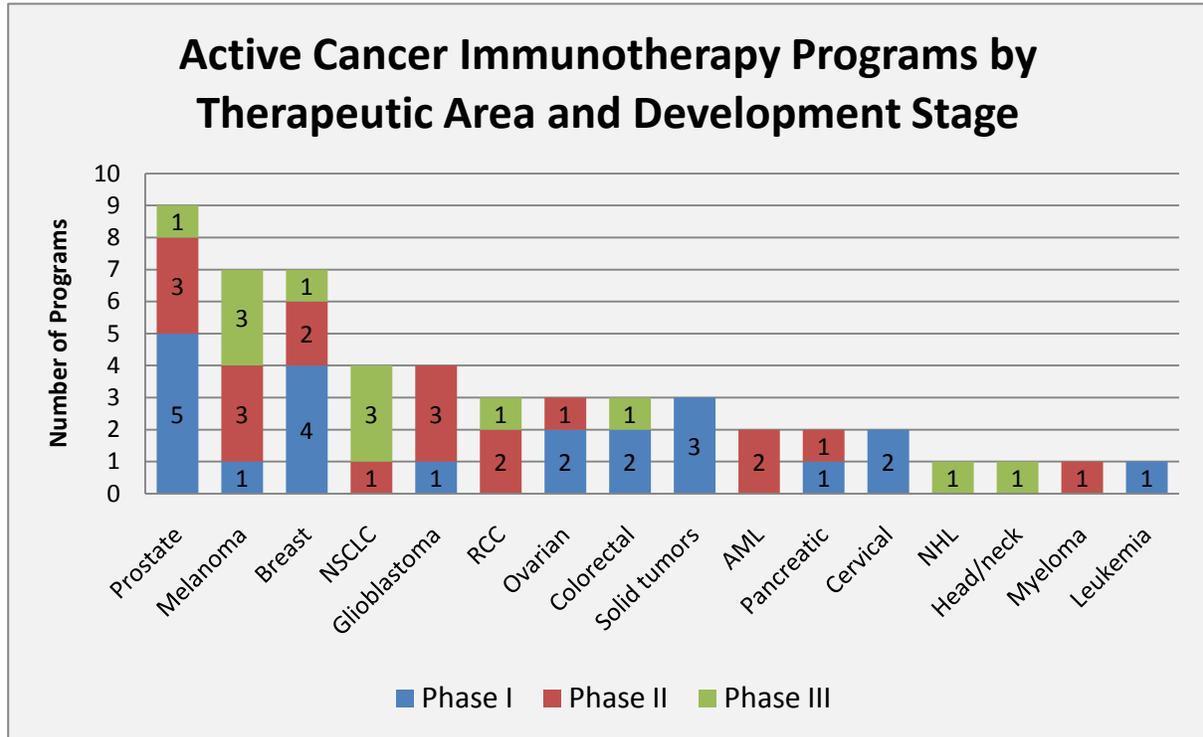
The second commercialization challenge will be assessing the cost/benefit profile of the vaccines. The IMPACT trial demonstrated that Provenge® increased survival by 4.1 months. In a perfect world, there is no price tag for extending life by a handful of months. Clearly many patients will demand access to a new biologic that has proven itself through the rigors of clinical testing. If and/or how much the payer is willing to spend is yet to be determined.

The final major commercialization challenge facing cancer vaccine companies is patient and physician acceptance. Many of the treatment modalities, especially autologous approaches, require specific patient populations treated by specialists. Specialized cancer treatment centers will be the site of the first few cancer vaccines approved. The success at these centers may indicate how the follow on vaccines are able to employ greater market penetration. In the long term however, a successful vaccine therapy will find its way to the many cancer centers (specialized and non-specialized) throughout the country.

## COMPETITION

There are more than 50 active immunotherapy programs in clinical trials by the companies referenced in this report (see **Figure 8**: Active Cancer Immunotherapy Programs by Therapeutic Area and Development Stage). Only five of these programs are for hematological malignancies, with the balance targeting solid tumors. Prostate cancer represents the largest segment of the market with 9 active clinical programs. Melanoma and breast cancer are tied for the second largest segment of with seven programs each.

FIGURE 8: ACTIVE CANCER IMMUNOTHERAPY PROGRAMS BY THERAPEUTIC AREA AND DEVELOPMENT STAGE



## PROSTATE CANCER

If approved by the FDA, Provenge® would represent the first active immunotherapy for the treatment of cancer – just as Rituxan® represented the first passive immunotherapy for the treatment of cancer. However, unlike Rituxan®’s market monopoly that lasted for nearly 12-years, Provenge® could face competition in a relatively short period of time. Nine active immunotherapy programs are in clinical development for prostate cancer – including a promising off-the-shelf vaccine called PROSTVAC that is set to begin a pivotal Phase III trial later this year (see **Table 8**: Potential 2010 Catalysts for Cancer Vaccine Companies).

Phase II trial results with PROSTVAC were recently published in the *Journal of Clinical Oncology*<sup>59</sup> demonstrating that at 3 years, prostate cancer patients treated with PROSTVAC had a better overall survival with 25 (30%) of 82 alive versus 7 (17%) of 40 controls, longer median survival by 8.5 months (25.1 versus 16.6 months for controls), an estimated hazard ratio of 0.56 (95% CI, 0.37 to 0.85), and stratified log-rank P = .0061. While the provocative data must be

confirmed in a larger phase III study, the Phase II results provide preliminary evidence of clinically meaningful benefit that appear to compare favorably with the Phase III results with Provenge® (see **Table 4**: Comparison of Trial Data for Provenge and PROSTVAC).

TABLE 4: COMPARISON OF TRIAL DATA FOR PROVENGE AND PROSTVAC

Company	Product	Trial/ Stage	Median Survival			3-year Survival	
			Control	Active	Difference	Control	Active
Dendreon	Provenge®	IMPACT	21.7 mo	25.8 mo	4.1 mo	32%	23%
Dendreon	Provenge®	Ph III	21.4 mo	25.9 mo	4.5 mo	34%	11%
Bavarian Nordic	PROSTVAC	Ph II	16.6 mo	25.1 mo	8.5 mo	30%	17%

While Provenge® may have first-to-market advantage, if the planned Phase III trial of PROSTVAC demonstrates similar efficacy to Provenge®, PROSTVAC has the advantage of being an allogeneic vaccine, which would be less costly to manufacture and easier to commercialize.

In terms of competitive advantage and parallels with the first passive cancer immunotherapy, Provenge® is also lacking a key ingredient that led to the commercial success of Rituxan®: a strong corporate partner. In March 1995, long before receiving FDA approval for Rituxan®, Idec formed a collaboration with Genentech, which helped validate the product.

Despite earlier efforts by Dendreon to partner Provenge®<sup>60</sup>, including a statement by the CEO that the company intended to sign a partner in the first half of 2004 and had narrowed it down to two suitors<sup>61</sup>, and at the time of this report's publication Dendreon does not have a commercial partner for Provenge®, which increases the commercialization risks.

## MELANOMA

Bristol-Myers Squibb, GlaxoSmithKline, and Vical each have pivotal programs underway for the treatment of melanoma (see **Table 5**: Melanoma Phase III Trials).

First to market is likely Bristol-Myers Squibb, which recently completed a three-arm, Phase III study comparing ipilimumab monotherapy, ipilimumab in combination with a gp-100 peptide

vaccine, and gp-100 peptide vaccine monotherapy. Data has been submitted for presentation at ASCO 2010 and Bristol-Myers may submit a BLA later this year for ipilimumab. In the Phase II trial for ipilimumab, overall disease control - defined as objective responses (complete and partial) and stable disease - was achieved in 19% (17/88) of patients. Of note, the overall incidence of immune related adverse events was 72% (63/88).

GlaxoSmithKline's MAGE-3 ASCI began enrolling patients in its Phase III melanoma trial (DERMA) in late 2008. GlaxoSmithKline uses genetic profiling of melanoma patients in predicting clinical outcomes of treatment with MAGE-A3 ASCI. In March 2010, GlaxoSmithKline and Abbott Laboratories (ABT) expanded their existing collaboration regarding the MAGE-A3 biomarker to include selecting patients for GlaxoSmithKline's investigational skin cancer immunotherapy. This may limit the market size to a subset of melanoma patients that overexpress MAGE-3, but could also result in increased efficacy for this group without the side effects observed with ipilimumab. Data presented at ASCO 2008 showed that the majority of reported adverse events with MAGE-3 were mild or moderate local or systemic reactions. According to ClinicalTrials.gov, GlaxoSmithKline's Phase III DERMA study is expected to finish by early 2014.

Vical is developing Allovectin-7<sup>®</sup>, a plasmid/lipid complex containing the DNA sequences encoding HLA-B7 and  $\beta$ 2 microglobulin, which together form a major histocompatibility complex, or MHC, class I. The company believes that injection of Allovectin-7<sup>®</sup> directly into tumor lesions directs an immune response against metastatic tumors through several mechanisms. Vical's partner, AnGes MG, Inc., is funding a pivotal Phase III trial being conducted under a SPA with the FDA. In January 2010, Vical announced the completion of enrollment in the Allovectin-7<sup>®</sup> trial. In order to effectively compete with Bristol-Myers Squibb and GlaxoSmithKline, Vical's Allovectin-7<sup>®</sup> must demonstrate superior safety, efficacy, and cost/benefit compared to its large pharmaceutical company peers.

TABLE 5: MELANOMA PHASE III TRIALS

Company	Product	Stage	Primary Endpoint	Category
<b>Bristol-Myers Squibb</b>	Ipilimumab with gp100	Ph III	Comparison of overall survival of ipilimumab alone and in combination with gp-100 versus gp-100 alone	Allogeneic, Peptide
<b>GlaxoSmithKline</b>	MAGE-A3 ASCI	Ph III	Disease Free Survival	Allogeneic, Peptide
<b>Vical</b>	Allovectin-7	Ph III	Variant of Progression Free Survival: Durable Response Rate	Allogeneic, Gene Transfer

## LUNG CANCER

GlaxoSmithKline, NovaRx, and Oncothyreon each have Phase III programs in NSCLC (see **Table 6: Lung Cancer Phase III Trials**).

First to market is likely GlaxoSmithKline, which is developing its MAGE-3 ASCI for NSCLC (in addition to melanoma). In the Phase II trial, the patient population selected for the presence of the predictive gene signature observed a 43% reduction in the relative risk of relapse. This positive data, presented at ASCO 2007 and 2008, led GlaxoSmithKline to initiate the 2,270 patient Phase III MAGRIT trial for patients with resected stage IB, II or IIIA NSCLC. GlaxoSmithKline may present preliminary results from this trial at ASCO 2010.

NovaRx started recruitment for their Phase III trial in mid 2008 after completion of their Phase II trial, which demonstrated a one-year survival of 61% and a two-year survival of 41%, and a median survival of 16 months. The trial is investigating Lucanix vs. placebo in patients with stage III and IV NSCLC. On November 4, 2009 NovaRx announced that the Company has successfully negotiated and received a SPA Protocol Amendment to the pivotal Lucanix® Phase III clinical trial allowing for the expansion of patients to include those with stable brain metastases.

GlaxoSmithKline and NovaRx are targeting different patient populations avoiding a short-term head to head competition. In addition, there is a potential for synergy between Lucanix and MAGE-3 due to their complementary mechanisms of action. GlaxoSmithKline appears to have

the most advanced clinical program, but similar to the melanoma MAGE-3 application, GlaxoSmithKline will only capture a percentage of the total market because of the necessity of patients to express the MAGE-3 antigen.

On March 23, 2010, Oncothyreon and its partner Merck Serono (a division of Merck KGaA) announced that they suspended Phase III trials of Stimuvax® (BLP25 liposome vaccine) for the treatment of NSCLC due to an unexpected serious adverse reaction in a patient with multiple myeloma. It is not yet clear when or if these trials will resume.

TABLE 6: LUNG CANCER PHASE III TRIALS

Company	Product	Stage	Patient Population	Primary Endpoint	Category
GlaxoSmithKline	MAGE-3	Ph III	Completely resected, stage IB, II or IIIA NSCLC	Disease-free survival	Allogeneic, peptide
NovaRx	Lucanix	Ph III	Stage IIIA (T3N2 only), IIIB or IV NSCLC.	Overall survival	Allogeneic, cellular
Oncothyreon	Stimuvax	Ph III	Unresectable stage III NSCLC	Survival duration	Allogeneic, peptide

## GLIOBLASTOMA

CellDex Therapeutics/Pfizer, Antigenics, and Northwest Biotherapeutics each have Phase II programs in development for GBM (see **Table 7: Glioblastoma Phase II Trials**).

First to market is likely CDX-110 by CellDex Therapeutics/Pfizer, which is an ideal allogeneic peptide vaccine due to the known role EGFRvIII plays in GBM and has potential to be effective in other EGFRvIII induced cancers such as neck squamous cell, cervical, renal cell, lung, prostate, bladder, colorectal, pancreatic, and breast cancer. With demonstrated efficacy, CDX-110 is likely to control the market share of those GBM patients who express this mutant receptor (24–67% of cases). According to ClinicalTrials.gov, the final data collection date for primary outcome measure is April 2010 and results are expected to be presented at ASCO 2010.

For those patients that do not express EGFRvIII, product differentiation will be determined by superior efficacy, as the other two late-stage cancer vaccines for GBM are both autologous

approaches. According to our roundtable discussion (see **Appendix A: Physician Roundtable Discussion**), physicians had a generally favorable opinion of the Antigenics technology but criticized the design of prior clinical trials. In October 2009, Northwest Biotherapeutics announced plans to begin a 240-patient Phase II clinical trial in GBM, but that the trial is not currently enrolling patients.

TABLE 7: GLIOBLASTOMA PHASE II TRIALS

Company	Product	Primary Endpoint	Category
<b>Celldex/ Pfizer</b>	CDX-110	Progression-free survival	Allogeneic, peptide
<b>Antigenics</b>	Oncophage	Overall survival	Autologous, peptide
<b>Northwest Biotherapeutics</b>	DCVax	Progression-free survival	Autologous, DCs

## THE FUTURE OF CANCER VACCINES

The complexities of trial design, delivery strategy, therapeutic area, and commercialization make it difficult to sift through all of the variables involved in determining the future potential of an active cancer immunotherapy product candidate. However, assuming Provenge® receives FDA approval; it will not only have a huge impact on men with CRPC, but may open the door for approval of other agents and advance the field of active cancer immunotherapy. In particular, it may facilitate combination trials with traditional chemotherapies and other treatments to improve clinical trial outcomes. The commercial introduction of Provenge® may also lead the way for next-generation, allogeneic therapies to reach the market.

While prostate represents the largest therapeutic areas for active cancer immunotherapy, the next wave of approvals will likely be spread out over several different cancers. For example, first-to-market active immunotherapy products likely include ipilimumab (with or without vaccine) in melanoma, BioVaxID® in NHL, MAGE-A3 ASCI in NSCLC, and CDX-110 in GBM. Over time as new immunotherapies enter the market within the same therapeutic area, product differentiation will be determined by efficacy, convenience and cost. Eventually, the top products could find their way as first line combination therapies if cost/ benefit are demonstrated.

Although the opinions of experts in field are mixed, it is likely that with new product approvals and advanced research, the field of active immunotherapy is poised for dramatic growth in the coming years. Using the history of passive immunotherapy development as a guide, it would not be surprising to see five active cancer immunotherapies approved within the next five years that revolutionize the treatment of cancer.

## POTENTIAL 2010 INDUSTRY CATALYSTS

TABLE 8: POTENTIAL 2010 CATALYSTS FOR CANCER VACCINE COMPANIES

Date	Company	Product	Disease	Catalyst
May 1, 2010	Dendreon	Provenge®	Prostate cancer	PDUFA date
June 4-8, 2010 ASCO annual meeting (abstracts released May 20, 2010)	Bristol-Myers Squibb	Ipilimumab w/ gp100	Melanoma	Ph III data
	GlaxoSmithKline	MAGE-A3 ASCI	Lung	Ph III data
	Celldex/Pfizer	CDX-110	Glioblastoma	Ph II data
	Celldex	CDX-011	Melanoma	Ph I/II data
	Celldex	CDX-1307	Epithelial	Ph I data
	Immunocellular	ICT-107	Glioblastoma	Ph I data
Q2 2010	Celldex	CDX-1307	Bladder cancer	Ph IIb initiation
	Immunocellular	ICT-107	Glioblastoma	Orphan drug approval
Q3 2010	Cel-Sci	Multikine	Head and neck	Ph III initiation
	Celldex	CDX-011	Breast	Ph IIb initiation
Q4 2010	Immunocellular	ICT-107	Glioblastoma	Ph II initiation
	Transgene SA/ Novartis	TG4010	Lung	Ph IIb/III initiation, potential SPA
2010	Advaxis	Cervical cancer	ADXS11-001	Ph II initiations
	Antigenics	Oncophage	GBM	Ph II results
	Bavarian Nordic	PROSTVAC	Prostate	Ph III initiation, potential SPA and Fast Track
	Bavarian Nordic	MVA-BM® HER2	Breast	Ph I/II initiation
	BioVest	BiovaxID	NHL	BLA filing
	Bristol-Myers Squibb	Ipilimumab w/ gp100	Melanoma	BLA filing
	Oxford Biomedica	TroVax	Renal Cell	Ph II initiation
	Vaccinogen	OncoVax	Colorectal	Ph III initiation
	Vical	Allovectin-7	Melanoma	Independent safety analysis

## APPENDIX A: PHYSICIAN ROUNDTABLE DISCUSSION

In mid-March 2010, MD Becker Partners conducted telephone interviews with several key opinion leaders in the area of cancer immunotherapy. Participants included:

- **James L. Gulley, M.D., PH.D., F.A.C.P.**, Director, Clinical Trials Group, Laboratory of Tumor Immunology and Biology & Senior Clinician, Medical Oncology Branch, Center for Cancer Research, National Cancer Institute National Institutes of Health
- **Susan Slovin, M.D., PH.D.**, Associate Attending Physician, Genitourinary Oncology Service, Sidney Kimmel Center for Prostate and Urologic Cancers, Department of Medicine, Memorial Sloan-Kettering Cancer Center, Associate Professor of Medicine, Department of Medicine at Joan and Sanford I. Weill Medical College of Cornell University
- **David Berd, M.D.**, National Director of Immunotherapy and Medical Oncologist, Cancer Treatment Centers of America, Eastern Regional Medical Center

A transcript of the discussion follows:

**MDB: Why has the field of active cancer immunotherapy been so challenging – how much of it relates to poor trial design?**

**Susan Slovin, M.D., Ph.D.:** In 1999, when GVAX first came out, there was a great deal of enthusiasm. However, look what happened with both VITAL-1 and VITAL-2 – they were negative trials in the Phase III setting. That was good science, but I think it boils down to bad trial design, similar to what we have seen with other immunotherapy product candidates.

**David Berd, M.D.:** Almost all of the vaccines that have reached final clinical testing have failed. A lot of them failed because they should have failed. For example, allogeneic vaccines, for which you use allogeneic tumor cells to stimulate immunity in every patient that has that histologic type of tumor, have never been shown to work in animal models. And the reason is they are based on the idea that there are one or more shared antigens. These are powerful rejection antigens and that you can immunize against them without too much trouble and then

you get immunity against many, many tumors of the same histologic type. And no one has even come close to showing that in animal models. And as a matter of fact, the Prehn stuff back in the 50s showed that that was not going to work. Sure enough, people just kept grasping to it and grasping to it, and it was funded to the tune of at least hundreds of millions of dollars and finally it failed.

Going back a little bit further, I am sure that you remember things like the GMK ganglioside vaccine, which got killed by being compared with interferon in melanoma and was shown to be inferior and basically that was the end of that business. It was the same kind of thing but now by taking a more sophisticated approach, by taking a chemical, which is expressed by virtually all melanomas, but also expressed by all kinds of other cells all over the body, including the brain and using this as a tumor antigen. And although the people who worked on this were smart and sophisticated, the idea just couldn't work and sure enough it didn't work. That was the first big shocker to the system. The failure of allogeneic vaccines came later.

In the second category of failure I would say were vaccines that really made sense but just for which the clinical development plan was so terrible that they essentially killed the technology. I would put in that category the Antigenics work. The heat shock protein stuff, which is an autologous vaccine, came directly out of Prehn's stuff because the guy that developed it was Pramod Srivastava who worked with Lloyd Old who was a buddy of Prehn and basically came out of there and adhered to those principles exactly. The animal work, which was published in places like *Nature* and *Science*, was beautiful work. I think the company then came along and performed the clinical trials, which made no sense, and, consequently, in my opinion, just wrecked the technology. This is probably not the first time in history that a good drug has been ruined by bad clinical development. One example of why it was bad clinical development is, with this particular vaccine, the dose was critical. And this was shown in animal models by the founder of the technology himself. If you gave too little or too much, you didn't get a therapeutic response. The company never ever did a dose finding study. The dose was always based on what you could conveniently harvest from the tumor. So they never really knew, even at the very end, whether they were giving the right dose, too little, or too much. Two out

of those three possibilities would have given them nothing, and they got nothing. If I had an unlimited amount of money I would resurrect the technology and do it the right way. I think it would work.

**James L. Gulley, M.D., Ph.D., F.A.C.P.:** Going back to GVAX, unfortunately that approach failed probably not because it wasn't a good product or an active product. If you look at VITAL-1, the hazard ratio was 1.01 when you compare patients who got vaccine versus chemotherapy and there was substantially less side effects. I think that perhaps if they had looked at patients who were a little bit less advanced, they may have had a positive trial. In a subgroup analysis based on some of the work we had done at the NCI where we had shown patients that had a predicted survival of at least 18 months, did better on vaccines. Cell Genesys looked at that and they found that indeed in VITAL-1 and in VITAL-2, if one look at just those patients with a predicted survival of at least 18 months, survival was better on the vaccine arms than those patients in the control arms.

The interesting thing is that looking at both the IMPACT study of Provenge® and our randomized Phase II multicenter study of PROSTVAC the median predicted survival (using the Halabi nomogram) was 21 months compared with VITAL-1, which was 16 months. You get the sense that if you treat patients with a lower tumor burden and a longer predicted survival, those are the patients that benefit the most from vaccines.

**MDB: Does this imply that vaccines are best studied in patients with earlier stage disease?**

**James L. Gulley, M.D., Ph.D., F.A.C.P.:** I think that what we are seeing is perhaps it is best to use the vaccine early enough in the disease course. Based on unpublished data from the NCI, it appears that with vaccines one is making an immune response that can lead to a sustained decrease in the angle on the growth rate. It's like compounding interest. The earlier you start saving, the bigger difference you will see. If you give a patient with really advanced cancer with only three months to live a vaccine, you aren't going to see anything there because you are only going to see a slight difference in the growth rate curve because you are at the finish line already – where if you start 10 years before that, you can potentially see a substantial improvement in survival. In a recently published trial, we noticed that in our patients that had

the lower tumor burden in our trials done here – those patients actually had a much greater improvement in survival compared with predicted survival based on a nomogram and seemed to derive the most benefit from the vaccine compared with those patients that had higher tumor burdens and shorter predictive survivals.

That goes hand in hand with the old bedtime story of the Tortoise and the Hare - slow and steady wins the race. You don't see these dramatic big declines in tumor burden but eventually over time, even if you don't see improved time to progression, you can see improved survival.

We are looking at a prospective trial designed to definitively answer this, but patients who get vaccines seem to do better on subsequent therapy. There are a lot of reasons why that may be. Certainly we and others have shown that subsequent therapies can alter the phenotype of the tumor, basically changing the way it looks to the immune system, making it easier for the immune system to either recognize or kill the tumor. It can act as a vaccine boost by killing some of the tumor cells. It can also actually enhance certain immune responses and decrease negative regulatory influences and can de-bulk the tumor and a lot of times tumors secrete negative regulatory cytokines or provide a haven for negative regulatory cells. Or the effect of subsequent therapies could be from combinations of all of the above.

#### **MDB: How does Provenge® differ from GVAX?**

**Susan Slovin, M.D., Ph.D.:** The philosophy is different. GVAX involves PC3 or LNCAP cell lines that were radiated and genetically transduced to produce GM-CSF. That's different than with Provenge®, where you take the patient's own cells and incubate them with prostatic acid phosphatase, which has been fused with GM-CSF. GVAX involves a prostate cancer cell line, while Provenge® involves the patient's own cells.

**David Berd, M.D.:** The GVAX approach originally was an autologous vaccine and was originally developed in mice. The animal work showed that in an autologous system that you could get an autologous vaccine to work completely autologous and the immunological trick in pushing it over the line was getting it to make large amounts of cytokine. They tested what was available at that time which was pretty much every cytokine which were known, which were

about I don't know 15 or 20. And they discovered that by far GM-CSF was the best cytokine to set up a cancer cell to make and the cytokine-producing cell became GVAX. Once a biotechnology company became involved, they found that it was a lot of trouble to make and so not only did you have to get autologous tumor cells but you had to transfect them with the virus that would allow them to make the GM-CSF. So they had big manufacturing problems from the beginning. They generated some very interesting results and had some cases of tumor regression and they had some Phase II data that were very promising. They just gave up on it. They just said we can't do this and made it into an allogeneic vaccine. I'm not saying there aren't some people that are still trying to use that in an autologous system but the company's products are almost all allogeneic. So, for example their prostate cancer studies which actually I haven't seen anything about it in for quite a while – there was no way they could get prostate cancer tissue in each patient and transfect it so they used prostate cancer cell lines and so the results they got were kind of ho-hum.

**MDB: Is there an opportunity to revisit the GVAX study in prostate cancer?**

**James L. Gulley, M.D., Ph.D., F.A.C.P.:** Yes, I clearly think that there should be. Celestia “Tia” Higano from University of Washington is looking at the overall survival follow-up from VITAL1 simply because a lot of us are saying we only had about 60 percent of the deaths (371 deaths / 621 enrolled) at the time of the non-prespecified futility analysis, let's follow this out because there is this late effect that we see with vaccines and perhaps the study will become positive later. At least we'll learn more about the effect of these vaccines. We can still learn a lot even if further follow-up reveals it is negative.

I know that Chuck Drake at Hopkins is planning a trial with GVAX in earlier patients, it was developed there, and the company that got the intellectual property rights is working with them. I understand that they are in the process of looking into making more vaccine. I know from both Cell Genesys and another company that made a whole tumor cell vaccine (Onyvax) that the LNCAP cells, which are part of the vaccine are difficult to grow.

**MDB: What is the impact on the field of active immunotherapy for cancer assuming that Dendreon's Provenge® product is approved?**

**Susan Slovin, M.D., Ph.D.:** On the one hand, it could be very helpful and open the door. On the other hand, it could close the door very, very rapidly if it doesn't pan out – similar to the experience with Iressa® (gefitinib), which reached the market and then was taken off. My biggest fear is that something like this may contaminate the market and not make it a better place.

**James L. Gulley, M.D., Ph.D., F.A.C.P.:** I think that is going to be a therapy that is approved soon and is going to generate a lot of interest in the field. Eventually we are going to find some of these off-the-shelf technologies are going to be able to generate similar types of responses and improvements in survival and perhaps may eventually supplant the more logistically complex autologous cellular products.

**David Berd, M.D.:** Provenge® is really interesting and I never would have thought it would have worked. But dendritic cells are very powerful. The company managed to set up a way of getting dendritic cells in which it looks like they do something. As you know, the data are not going to be a wipe out. I am hoping that the data are positive. We are just hoping that they get over the finish line and get a result that the FDA considers to be worthy of marketing, but it is going to be a small effect size and that they have designed the clinical trial so they can detect the relatively small effect size.

Also, the success of Provenge® is going to depend on how much it costs, what insurance companies pay for it, whether Medicare pays for it. It is a fair amount of trouble to administer. People always commented on the trouble to administer other autologous vaccines, such as MVAX, but it's actually fairly easily. You could actually sell 10,000 doses a year and very easily train the users into administering MVAX correctly. In contrast, Provenge® is a lot of trouble. You have to leukapheresis people, you send them the cells, the Company grows the dendritic cells, they pulse them with antigen, and they send them back to you and they have to be administered intravenously in a very certain way. So, they are already in the process of very carefully selecting which medical centers, and I think they are going to mainly be medical

centers, are going to be able to buy Provenge®. I don't think they are just going to sell it to any physician who wants it. I don't know if the FDA is involved in telling them who then can sell it to and whom they can't. But I think the people who run the company, at least initially, want to make sure this is in the hands of people who know what to do with it, which is going to be a highly selective group. I know people are already trying to position themselves to be in the groups that will be able to get this stuff for their patients that hopefully will be paid for by somebody. That doesn't take away from the triumph of Provenge®. I mean if they have a positive study and it gets FDA approved, I and almost everybody else will be very excited for it. It will be very good for the biotech industry. But it's not going to be a Salk vaccine. You'll be able to get in front of investors and say, "Look, this thing works; finally someone did it right and got it to work, so give us \$100 million and we'll get our technology to work better."

There are some analysts who have said that all of the attention on influenza vaccines actually had some positive effect on funding for cancer vaccines. I'm not sure if that is true because I am not out there raising money anymore. But investors do tend to generalize from one immunotherapy to another.

**MDB: There is a lot of discussion regarding the fact that Provenge® demonstrated a survival benefit without any anti-tumor effect. How do you reconcile this?**

**Susan Slovin, M.D., Ph.D.:** For some people, this is considered a new paradigm in the world of FDA by approving a drug based on survival, but with no anti-tumor effect. I am not convinced that survival in the absence of anti-tumor effect is the right end point. In other words, changes in circulating tumors cells or changes in markers of bone turnover, something that truly reflects the inherent biology of the tumor. A purist in the immunological world would expect to see an anti-tumor effect, but the absence of a biologic readout has been the major problem with most of the immunotherapies. You can demonstrate anti-tumor immunity *in vitro* with an enzyme-linked immunospot assay (ELISpot) or enzyme-linked immunosorbent assay (ELISA), but that does not seem to correlate with the biologic effect. That's the problem in terms of acceptability. If I saw a 50% reduction in a large tumor, I might feel differently.

**James L. Gulley, M.D., Ph.D., F.A.C.P.:** It's clearly something that is vital for us to understand. Briefly, we need to remember that when we are looking at therapeutic vaccines, all the rules we learned with conventional therapies may not apply. For instance, therapeutic vaccines directly target the immune system, not the tumor or its microenvironment. Then the immune system in turn can target the tumor and its microenvironment. Therapeutic vaccines often have a delayed response, probably in part because of that. Whereas with conventional therapies we expect responses with peak level of drug we should start to see tumor cell killing.

With therapeutic vaccines you can generate immune memory, and this can lead to long lasting responses. All of those play into the kinetics of a clinical response following a therapeutic vaccine being completely different to the kinetics of a clinical response following a conventional therapy.

With conventional therapy, during treatment you have a dramatic decrease in the tumor growth rate and if it is an effective therapy, the tumor volume goes down. However, when the tumor starts to progress on that therapy, the tumor growth rate goes back to the identical growth rate that it was on before the therapy.

With therapeutic vaccines however, we don't see dramatic decreases in the tumor volume. And this has been known for a long time. Most of the patients we treat don't have substantial shrinkage of tumors, although we do see those. Those are relegated to the 5% -10% range, not to the percentage where we say most chemotherapy drugs are active.

We might not even see improved time to progression due to delayed effect of these immune responses. But what we do see is, and this is studies we did here in prostate cancer looking at conventional therapy versus immunotherapy, we do see a delayed effect on the tumor growth rate where there is a continued sustained downward negative pressure on the tumor growth rate.

The only place we have seen this is with vaccine clinical trials we see a substantially delayed tumor growth rate following vaccination. And sometimes this is not seen while in the three or four months on study, this often is not noticed until afterwards. We have analyzed over 50

patients now with this and it's pretty interesting the differences that we have observed before study, during study and the delayed suppression of the growth rate following study. We have a paper that we are finishing writing up now that outlines this.

**David Berd, M.D.:** A long time ago, maybe 8 years ago, no one would take you seriously if you said you had a treatment that had antitumor effects, but did not shrink tumors. So, in other words in the RECIST criteria or the many measuring systems that preceded the RECIST criteria, tumor regression was considered valuable and always very often associated with improved survival but what is known as stable disease was not worth mentioning. It was considered an observation that could not be corroborated, and the fact that you watched the patient and tumor did not grow for awhile just meant you had slow growing tumors. When I just first starting publishing in the area, we saw a lot of people with stable disease after receiving autologous vaccines. No reviewer would take that data seriously. Now all of a sudden you have a large number of drugs, most of them not immunological, most of them are these are targeted agents these tyrosine kinase inhibitors that seemed to prolong survival (although usually very modestly) but don't induce tumor regression. It is amazing how casually the oncologic community has suddenly accepted this. To make it sound scientific, people have developed the concept of "progression free survival" to measure effectiveness of treatments that prolong survival but don't cause tumor regression., Many people had thought about this concept for years but their ideas and their papers were rejected; now their time has come, I guess.

It certainly is reasonable that an immunological treatment, for example, Provenge®, which is a pretty weak treatment, could work by causing a very small number of tumors to shrink and preventing a large number of tumors from growing much, and ending up with a small but significant advantage in progression-free survival. To me that is not a great result, but, at this point in history, might be acceptable to the oncological community and to the FDA. It's strange to think that the work in the tyrosine kinase inhibitors has tremendously helped immunologists in that it has allowed them to use a measure of effectiveness that nobody would allow them to use before.

**MDB: Is the bottom line that Provenge® demonstrated a survival advantage?**

**James L. Gulley, M.D., Ph.D., F.A.C.P.:** Yes, exactly and it met all its endpoints as pre-specified in the special protocol assessment (SPA). We should hear by May 1.

**MDB: To what extent does GM-CSF alone play a role in the efficacy of Provenge® and other cancer vaccines?**

**James L. Gulley, M.D., Ph.D., F.A.C.P.:** Probably little from free GM-CSF because in the product they give back with the Provenge®, all of that's washed and so there's no external GM-CSF – it's only what's been internalized by the antigen presenting cells in the product.

**Susan Slovin, M.D., Ph.D.:** It is a potential concern. Recall in the 1980s that Steven Rosenberg pioneered a vaccine approach using autologous lymphokine-activated (LAK) killer cells in combination with interleukin-2 (IL-2) for the treatment of melanoma and kidney cancer. However, in the clinical trials there was an increased rate of objective response and long-term survival in patients receiving IL-2 alone, indicating that the anti-tumor effect was mainly due to the IL-2, not the vaccine.

**MDB: What would be the impact of a delay in approving Provenge®?**

**David Berd, M.D.:** In the clinical world, not being approved or being delayed for some very serious reason would have very little impact. I don't think most clinicians are waiting with bated breath to see how this turns out. In the business world, delay would be a holocaust. Even if it's something to be fixed, if it requires doing another trial, that might be the end of the technology. I mean, if it requires changing the color of the label that's one thing. But if somebody at FDA finds something basic they don't like about this, I can't imagine Dendreon being able to find the money or interest to start all over again. After how many years of development and how many hundreds of millions of dollars? After coming so close that would definitely be a heart breaker.

**MDB: How big of a challenge is the autologous nature of Provenge®?**

**Susan Slovin, M.D., Ph.D.:** When the data was presented at the American Urological Association (AUA) meeting a year ago, everybody was under the impression that this would be used by an urologist in a first line setting post hormonal therapy or when there was a change toward metastatic disease. Autologous therapies requires a lot of preparation and I don't foresee the urologist doing a leukapheresis, so they're going to have to get involved with a blood banking center to make everything work.

**David Berd, M.D.:** With any autologous vaccine there are manufacturing issues. You still have to get enough cells, you have to extract the proteins, and they go on and on. There are manufacturing issues with Dendreon's product, which are enormous. It is a tremendously expensive product to make. Obviously that was not enough to dissuade investors from coming in if they thought it was going to work. My idea has always been that using autologous vaccines was only going to be a kind of temporary technology anyway. Once you got autologous vaccines on the market and people accepted them as effective, then you would find the real antigens. Hopefully there wouldn't be a different antigen for every different cancer, but there would be a family of antigens, of maybe 5, 10, 20 or 30. Each tumor, say each melanoma, probably expresses one of those antigens or maybe in some cases more than one. You could type the tissue and give the patient the pre-made vaccine containing the antigens required. This has now become known as personalized medicine is something that everybody wants to do. The molecular people have been way ahead of immunologists in pursuing this strategy. I never imagined that for the next one hundred years, people would have to get autologous vaccines with all the trouble of obtaining sufficient cells and having to do the surgery on each patient. Instead, I assumed that once you established autologous vaccines, the next technologic advance would take you to a system where manufacturing (extracting and cloning antigens) was a trivial issue. So you would essentially have off the shelf vaccines, which would not have been possible without passing through the intermediate step of the autologous cellular vaccine.

**MDB: That implies that an off-the-shelf vaccine would be preferred over an autologous approach?**

**Susan Slovin, M.D., Ph.D.:** I think for many patients it would be, because they want something that can be administered easily and on a rather infrequent schedule.

**James L. Gulley, M.D., Ph.D., F.A.C.P.:** I like the idea of an off-the-shelf type of approach because logistically and economically it is much simpler. You don't have to worry about where to get a pheresis or if you are within an 18 hour turnaround time for getting a product to a central processing facility. Some of these logistical concerns completely evaporate when you are using an off-the-shelf technology where you simply take remove it from the freezer, thaw it and inject it into the patient, but clearly it's going to be several years before we get results from any trial that has started now.

**MDB: How soon might Provenge® face competition from off-the-shelf vaccines or other competitors?**

**James L. Gulley, M.D., Ph.D., F.A.C.P.:** Well, I think that at least for prostate cancer we are not going to see any data for three or four years for competing vaccines. Right now, the PSA TRICOM or PROSTVAC is the furthest along in development for prostate cancer after Provenge®.

**MDB: What should be done from a clinical development perspective to advance the field of active immunotherapy?**

**Susan Slovin, M.D., Ph.D.:** In general, cancer vaccines as single agents don't work. They need to be tested in combinations, but the problem is that we don't know the right combinations. It might be chemotherapy plus the immune therapy or two different kinds of immune therapy so that different signaling pathways are being hit. At this point, nobody knows the right answer.

**James L. Gulley, M.D., Ph.D., F.A.C.P.:** I think that we are going to have to come in with other combinations, especially with more advanced disease. I think with vaccines alone we are shooting blanks in patients with very advanced disease. The T cells might be able to get to the

tumor but the tumor is so acidic, so depleted of nutrients. You have to do multiple therapeutics to really get the T cells to be able to work at the site of the tumor. Even if you generate beautiful T cell responses, they still need to be functional at the site of the tumor. So, one idea is to combining vaccines with drugs that normalize the blood flow to the tumor, like angiogenic drugs are thought to do. They decrease neovascularization and eventually do starve the tumor. But they initially are thought to normalize the blood flow and improve the delivery of chemotherapy to the tumor. It allows for better nutrient environment in the tumor, therefore potentially better function of T cells within the tumor. Paradoxically, something that could on one hand appear to be helping the tumor normalize the blood flow, it actually could lead to better chemotherapeutic responses and immunologic responses. We have also completed clinical trials showing one can safely give vaccine and radiation or chemotherapy and still generate immunologic responses.

**MDB: Tell us about other active immunotherapy approaches for prostate cancer.**

**James L. Gulley, M.D., Ph.D., F.A.C.P.:** We're working with PROSTVAC or PSA TRICOM, which are used interchangeably. We had a paper that came out online in the *Journal of Clinical Oncology* last month, showing in a randomized, multicenter phase II study an overall survival advantage. Now that was not the primary endpoint of the study, but it was interesting to see that there was an 8.5 month improvement in overall survival with a hazard ratio of .56. It's a pretty big effect size seen at least in that study. We plan on doing a three arm, multi center randomized Phase III global trial with 1,200 patients looking at overall survival as the primary endpoint. The three arms are vaccine with recombinant GM-CSF versus vaccine alone versus empty vector placebo.

**MDB: Wasn't TRICOM being developed by an industry partner?**

**James L. Gulley, M.D., Ph.D., F.A.C.P.:** Yes, Therion Biologics, based in Cambridge, MA. Problem was they needed money, so they went with largely one investor and they decided to pursue a very aggressive clinical trial strategy. They went with another vaccine (PANVAC) directly from a 10 patient phase I trial into a multicenter phase III trial in patients that had failed gemcitabine with pancreatic cancer that had on average 2 to 3 months to live and did a trial

there hoping to hit a home run with this PANVAC vaccine. We could have saved them about \$100 million dollars. It was clearly a futile attempt and they burned through money too quickly. The investors pulled the plug and they became insolvent and basically all of the intellectual property reverted back to the NCI because we were the ones who developed the technology in the first place. This was 2006 when this happened and it's only now that we have been partnering with this new company for a year and a half and they're currently making vaccine for the Phase III trial.

**MDB: What is the company you are currently working with?**

**James L. Gulley, M.D., Ph.D., F.A.C.P.:** The company that we are currently partnered with to make the vaccine is BNIT (Bavarian Nordic), which makes the small pox vaccine, the MVA vaccine. Those are the "safe" small pox vaccines. And they have a contract with the US government for several million doses of these smallpox vaccines. Infectious disease vaccines was originally their primary strategy, but now with these results they are moving heavily into the cancer vaccine realm and probably will partner with us on one of our other pox viral vaccines that targets CEA and MUC-1 and has the three co-stimulatory molecules (PANVAC). Their lead agent is PSA TRICOM, which hopefully will be starting in a Phase III trial later this year and they will be sponsoring that.

**MDB: How would you compare and contrast the various active immunotherapies being developed for prostate cancer?**

**James L. Gulley, M.D., Ph.D., F.A.C.P.:** There's the cellular product, which are largely antigen presenting cell-based like Dendreon. There are whole tumor cell vaccines, of which GVAX was clearly out front in prostate cancer. It was nice because it was genetically engineered to secrete GM-CSF locally, not systemically. At the local injection site GM-CSF could help dendritic cells migrate to the area and mature. Then there's the PROSTVAC, the pox viral vector. There are also DNA based vaccines. Doug McNeil has published a very nice paper last year on a prostatic acid phosphatase DNA-based vaccine study, but that was just a phase I study. There have also been peptide based vaccines.

But as far as what has made it through Phase IIB or Phase III trials, there really are those three PSA TRICOM, GVAX and Provenge®. The differences between the GVAX and PSA TRICOM are that they are both off-the-shelf, but the GVAX does have a shorter half life, about three months compared with more than 10 years for the pox viral vectors. It does have to be shipped in liquid nitrogen, not terribly difficult, but if you are going to have to replace a supply every three months, it is a little bit more logistically complex, but clearly not nearly as logistically complex as Dendreon's platform.

As far as which vaccine works better than the other in terms of inducing immune responses, it is difficult to look at immune response to whole tumor cell vaccines, at least T cell responses, because you don't really know what's the best antigen to look for. There could be immune response to a wide variety of different tumor associated antigens. That becomes a little bit of an issue when doing initial studies proving immunogenicity. You can look at the local injection site reactions, which were quite brisk with this, but it makes it easier when you have a target you know is present in the vaccine that you are trying to elicit an immune response for that you can measure that - like with PSA TRICOM, it's PSA and with the Dendreon vaccine it's the PAP or the fusion protein.

It's just a little but more difficult with GVAX to measure T cell responses because you don't know what really matters. People have looked for prostate specific T cells (PSA, PSCA, PAP, etc) and there is hardly anything there. Pretty soon you run out of T cells from the patient. You don't know what is the best antigen to look for and it may be that for each patient that you generate an immune response generates an immune response to a slightly different target and that is what is more relevant for that patient. In none of these trials have we shown any surrogate immune point that correlates with clinical outcomes. But at least we have been able to look at T cell responses in the Provenge® and PSA TRICOM. In GVAX they looked at antibody responses in GVAX but not really any T cell responses, because we don't know what to look for.

**MDB: We discussed the issue of poor trial design earlier, what do you think about the fact that some active immunotherapy trials are still looking at progression free survival (PFS) versus overall survival?**

**James L. Gulley, M.D., Ph.D., F.A.C.P.:** Difficult in prostate cancer. I think they (FDA) would accept, and in fact I have had preliminary discussions with them, a properly designed clinical trial looking at prevention of metastatic disease. For example, someone that has castrate resistant prostate cancer that has no evidence of metastatic disease, if you can prevent or delay time to metastatic disease, that is potentially a registration endpoint. I think progression free survival is somewhat problematic in prostate cancer because what are you going to call progression? Most people don't have soft tissue disease, so then it becomes bone lesions and the only thing you have to measure is a bone scan. It's a lot easier to look at progression free survival in breast cancer and in colorectal cancer, and time to metastatic disease is reasonable, but I think for prostate cancer it makes it a lot more difficult.

**MDB: In view of immune tolerance is CTLA-4 a promising opportunity and are there any adjuvants that look promising?**

**David Berd, M.D.:** CTLA-4 is, from an immunologist's point of view, a breakthrough technology. Whether it is also a breakthrough in clinical care is debatable. People talked about suppressor cells as inhibitors of immunity, particularly weak immunity like tumor immunity, going back for 30-40 years, maybe a little after Prehn. For a long time many eminent scientists did not believe that they existed. People used to stand up in meetings to say that there is no such thing as suppressor cells so don't waste your time studying them. The clinical trials and animal work with this antibody, or probably with the series of antibodies, really showed there are suppressor cells that suppress the immunity. If you damage these cells with the antibody you can get immune responses to things that you otherwise wouldn't respond to. So that has fit in very well. We have always used cyclophosphamide to inhibit suppressor cells because cyclophosphamide was shown to work in that way long before people had identified the phenotype of suppressor cells. Now that they have been identified and antibodies against them are available, you have a newer way of doing it. Whether it is a better way is not clear.

Because as it turns out, I think to everyone's surprise, is that when you start knocking off suppressor cells the first thing that happens is not tumors melting away. The first thing that happens is development of autoimmunity against normal antigens – people getting all kinds of auto-immune diseases. The second thing that sometimes happens is that tumors shrink. No one thought it was going to be that way. Everyone thought it would work in the opposite order. It was a shock and a little bit of a disappointment. It has really been an eye opener to how the immune system works and how it regulates the response to tumor antigens. And still no one really has figured this out. People are just so busy doing clinical trials and making interesting clinical observations. I don't think anybody has had time to think it through and to explain why it does what it does. To me it is very surprising and should make everybody start questioning their ideas about tumor immunity.

**MDB: There are vaccines in development for ovarian and other cancers, tell us about some work in this area.**

**David Berd, M.D.:** We're doing a Phase I/II study in advanced ovarian cancer with OVAX, an autologous, hapten-modified cellular vaccine. People with ovarian cancer die with stage three because it stays in the abdominal area. Usually it does not spread through the blood stream to places like the lung and bones and brain. The patients could have stage 4 but almost all the patients have stage 3. Of course, it is a very extensive disease within the abdomen so it's a very extensive stage 3, but that is the stage. In order to increase the chance that patients could have a response, de-bulking of the tumor, both physically and chemically is an important prerequisite for the current trial. So these are patients who undergo a surgical de-bulking, which is a very common modality used even in very late ovarian cancer, in which surgeons remove almost all of the tumor they can see, leaving only very tiny pieces if possible. Then they get 4 weeks of intraperitoneal chemotherapy with either Taxol or Taxotere, to try and clean up the situation even more. And then they get OVAX. So they have advanced disease, but we are trying to give it in a situation in which we have a shot at getting a clinically meaningful response because you have lowered the tumor burden. Everybody agrees that tumor burden is the limitation in immunotherapy.

The only prior studies that were done were at Jefferson, which were presented at ASCO around 2000/2001 was in a small number of patients. There were a couple of patients who had significant antitumor responses that were pretty impressive. The immunological data looked really good. But these of course were vaccines not produced under GMP, so once you convert to a GMP process, from the point of view from the FDA, is a different product. OVAX, although very close to what we did ten years ago, is not what we did ten years ago. It's almost starting over. But since toxicity is expected to be a very small issue, the FDA let's you do a Phase I/II trial in which you are measuring effectiveness at least immunologically at the same time that you are collecting safety data.

The trial also looks at three doses of OVAX. The three doses that are being looked at come from the melanoma trial. There were many dose trials of the melanoma vaccine before it was called MVAX. A dose trial was completed by AVAX and there was a clear dose response, something that has very rarely been shown by any tumor vaccine in clinical trials. It's something that has rarely been shown outside of the AVAX trial. We are testing the same dosage range for OVAX, and the same schedule of administration that we found optimal for MVAX. It's not a randomized trial. The dose is determined by the manufacturing facility and the number of cells that are able to be extracted by the tumor but it is a blinded trial. The major readout is immunological, but we expect some meaningful clinical results.

## APPENDIX B: PHYSICIAN BIOGRAPHIES

### JAMES L. GULLEY, M.D., PH.D., F.A.C.P.

Director, Clinical Trials Group, Laboratory of Tumor Immunology and Biology &  
Senior Clinician, Medical Oncology Branch  
Center for Cancer Research, National Cancer Institute National Institutes of Health

Dr. Gulley is a board-certified medical oncologist and director of the Clinical Trials Group within the Laboratory of Tumor Immunology and Biology at the National Cancer Institute (NCI). He is also a senior clinician within the Medical Oncology Branch. He received his medical training at Loma Linda University in its medical scientist training program where he obtained a Ph.D. with his work in tumor immunology as well as an M.D. He went to Emory University for a residency in internal medicine and then to NCI for a fellowship in medical oncology. Following his fellowship, he was retained as senior staff within NCI. Dr. Gulley has run multiple clinical trials in immunotherapy since 1999 and is an internationally recognized expert in this field.



NCI's Center for Cancer Research (CCR) is currently conducting the following trial(s) for patients with breast, lung, or prostate cancer.

- An Open-Label Phase I Study to Evaluate the Safety and Tolerability of a Vaccine Consisting of Whole, Heat-Killed Recombinant *Saccharomyces Cerevisiae* (Yeast) Genetically Modified to Express CEA Protein in Adults With Metastatic CEA-expressing Carcinoma (NCI-09-C-0101)
- A Randomized Phase II Trial Combining Vaccine Therapy With PROSTVAC/TRICOM and Flutamide vs. Flutamide Alone in Men With Androgen Insensitive, Non-Metastatic (D0.5) Prostate Cancer (NCI-07-C-0107)
- A Randomized Phase 2.5 Study of [153]Sm-EDTMP (Quadramet) With or Without a PSA TRICOM Vaccine in Men With Androgen-Insensitive Metastatic Prostate Cancer (NCI-07-C-0106)
- A Randomized Pilot Phase II Study of Docetaxel Alone or in Combination With PANVAC-V (Vaccinia) and PANVAC-F (Fowlpox) in Patients With Metastatic Breast Cancer (NCI-05-C-0229)

## SUSAN SLOVIN, M.D., PH.D.

Associate Attending Physician, Genitourinary Oncology Service, Sidney Kimmel Center for Prostate and Urologic Cancers, Department of Medicine, Memorial Sloan-Kettering Cancer Center

Associate Professor of Medicine, Department of Medicine at Joan and Sanford I. Weill Medical College of Cornell University

Dr. Slovin is Associate Attending Physician in the Genitourinary Oncology Service, Sidney Kimmel Center for Prostate and Urologic Cancers, Department of Medicine, Memorial Sloan-Kettering Cancer Center, and Associate Professor of Medicine, Department of Medicine at Joan and Sanford I. Weill Medical College of Cornell University. She earned her doctorate in pathobiology from Columbia University and her medical degree from Jefferson Medical College in Philadelphia, Pennsylvania. Her postdoctoral training included a fellowship in clinical immunology through Scripps Clinic & Research



Foundation, La Jolla, California; an internship and a residency in internal medicine from The Mount Sinai Hospital in New York; and a hematology/oncology fellowship in the Department of Medicine, Memorial Sloan-Kettering Cancer Center. She is a board-certified medical oncologist with expertise in the areas of prostate cancer immunology and clinical trial design. A noted immunologist, she has been leading an initiative which focuses on the development of novel immunologic approaches for the treatment of prostate cancer. This includes assuming the leadership of the Prostate Immunotherapy Group (PIGs) sponsored by the Prostate Cancer Foundation whose challenge is to develop guidelines for development of immune therapy clinical trials in prostate cancer. She is a member of several professional associations, including the American Association of Immunologists, American Association of Investigative Pathology, and American Association of Cancer Researchers, American Urologic Association and Sigma Xi Research Society. An ad hoc reviewer for numerous journals, including Cancer, Cancer Immunology and Immunotherapy, JAMA, Cancer Research, and Clinical Cancer Research, Urology and Journal of Urology, she also serves as Associate Editor for Seminars in Oncology as well as the editorial boards of several major journals including Clinical Cancer Research. She is also an ad hoc reviewer for NIH and DOD grant study sections. Dr Slovin has is well-recognized in the area of prostate cancer immunotherapy and has contributed many peer-reviewed articles and reviews to the medical literature. She has received numerous accolades and was recognized by CancerCare as the 2003 Physician of the Year. She was the keynote speaker in 2008 at the Massachusetts Prostate Cancer Coalition.

## DAVID BERD, M.D.

National Director of Immunotherapy and Medical Oncologist  
Cancer Treatment Centers of America  
Eastern Regional Medical Center

Board certified in medical oncology and internal medicine, Dr. Berd earned a Bachelor of Science degree from Pennsylvania State University, before attending Jefferson Medical College in Philadelphia. After earning his medical degree, Dr. Berd completed both an internship and residency at the Hospital of the University of Pennsylvania.

In 1970, Dr. Berd moved from Philadelphia to Atlanta, Georgia to work for the U.S. Public Health Service in the Center for Disease Control and Laboratory branch. During his military service, he also taught at the Emory University School of Medicine.



After two years in the South, Dr. Berd migrated to New Haven, Connecticut and completed a fellowship in medical oncology at the Yale University School of Medicine. He subsequently completed a National Institutes of Health (NIH)-funded research fellowship at Yale.

Prior to joining CTCA, Dr. Berd worked as an attending physician at Thomas Jefferson University Hospital, where he had taught since 1991. He also spent nine years as a research physician at Fox Chase Cancer Center. Most recently, Dr. Berd served as the Chief Medical Officer for AVAX Technologies, Inc.

Over the course of his career, Dr. Berd has published 83 papers in numerous medical journals alongside dozens of editorials, reviews and abstracts. He has also attended numerous conferences, seminars, and over 100 lectures by invitation.

In June 2008, Dr. Berd joined CTCA. According to Dr. Berd, the combination of choices, cutting-edge therapies, and hope sets CTCA apart from other cancer hospitals. One of his first initiatives since joining CTCA is an experimental cancer vaccine, which is currently being tested in patients with ovarian cancer.

Dr. Berd is a member of eight professional societies, including the American Association for Cancer Research, the American Society for Clinical Oncology, the American Association for the Advancement of Science, and the American Association of Immunologists. He also serves on review committees for various government advisory groups.

TABLE 9: SELECT CANCER VACCINE COMPANIES AND PROGRAMS

Company	Product(s)	Partner	Stage	ClinicalTrials.gov Identifier	Disease	Category	Strategy	Description
Advaxis (ADXS.OB)	ADXS11-001		Ph I	n/a	Cervical	Autologous	Cellular	Whole cell bacteria ( <i>Listeria monocytogenes</i> ) directed against HPV-16-E7 stimulates innate immunity
Alphavax (private)	PMSAvrp CEA		Ph I Ph I	n/a NCT00529984	Prostate Colon	Allogeneic	Gene Transfer	DC targeted with virus-like replicon particles expressing tumor specific antigens, such as PSMA or CEA
Antigenics (AGEN)	Oncophage		Ph II	NCT00293423 NCT00905060	Glioblastoma	Autologous	Peptide	gp96 heat shock protein-peptide complex
Aphera (private)	NeuVax		Ph II Ph II	n/a n/a	Breast Prostate	Allogeneic	Peptide	E75 peptide derived from HER2
Argos Therapeutics (private)	AGS-003		Ph II	NCT00678119 NCT00272649	Renal Cell	Autologous	DCs	Patient's DCs are transfected with their own tumor RNA and then reintroduced
Avax (AVXT.PK)	Mvax LungVax Ovax		Ph III Ph I/II Ph I/II	NCT00477906* NCT00298298* NCT00660101	Melanoma NSCLC Ovarian	Autologous	Cellular	Whole tumor cells are isolated and the antigens are chemically modified by haptization prior to reintroduction
Bavarian Nordic A/S (OMX: BAVA)	PROSTVAC MVA-BN PRO MVA-BN HER2	NCI	Ph II Ph I/II Ph I/II	NCT00078585 n/a n/a	Prostate Prostate Breast	Allogeneic	Gene Transfer	PROSTVAC uses two different poxviruses that each encode PSA plus three co-stimulatory molecules

Company	Product(s)	Partner	Stage	ClinicalTrials.gov Identifier	Disease	Category	Strategy	Description
BioSante (BPAX)	GVAX		Ph II Ph II	NCT00727441 NCT00426205	Pancreatic AML	Allogeneic	Cellular	Whole tumor cell lines are isolated and engineered to secrete GM-CSF
BioVest International (BVTI.PK)	BiovaxID		Ph III	NCT00091676	NHL	Autologous	Peptide	Purified peptides from each patient are coupled with GM-CSF and KLH
Bristol-Myers Squibb (BMY)	Ipilimumab plus gp100		Ph III	NCT00094653	Melanoma	Allogeneic	Peptide	Human monoclonal antibody targeting CTLA-4 with or without gp100 peptide vaccine
Cel-Sci (CVM)	Multikine		Ph III	n/a	Head and Neck	Allogeneic	Peptide	Mixture of interleukins, interferons, chemokines, and colony-stimulating factors that simulate the body's immune response
CellDex Therap (CLDX)	CDX-110	Pfizer Inc. (PFE)	Ph II	NCT00458601	Glioblastoma	Allogeneic	Peptide	Peptide targeting EGFRVIII with KLH
Cytos Biotechnology (SIX:CYTN)	CYT004		Ph II	NCT00651703	Melanoma	Allogeneic	Gene Transfer	MelQbG10 carrier expressing MART-1
Dendreon Corp. (DNDN)	sipuleucel-T lapuleucel-T		Ph III Ph I	NCT00065442 n/a	Prostate Breast	Autologous	DCs	DCs co-cultured with a recombinant fusion protein of PAP and GM-CSF
Generex Biotech (GNBT)	AE37		Ph II Ph I	NCT00524277 n/a	Breast Prostate	Allogeneic	Peptide	Peptide targeting li-Key/HER2/nue
Genitope Corp. (GTOP.PK)	MyVax		Ph III	n/a, failed	NHL	Autologous	Peptide	Isolated tumor antigen peptides coupled with GM-CSF and KLH
Geron Corp. (GERN)	GRNVAC1		Ph II	NCT00510133	AML	Autologous	DC	DCs pulsed with RNA for hTERT and LAMP

Company	Product(s)	Partner	Stage	ClinicalTrials.gov Identifier	Disease	Category	Strategy	Description
GlaxoSmithKline plc (GSK)	MAGE-A3 ASCI		Ph III	NCT00480025	Lung	Allogeneic	Peptide	A recombinant fusion protein derived from the melanoma antigen MAGE-3
			Ph III	NCT00796445	Melanoma			
			Ph II	NCT00706238	Melanoma			
			Ph II	NCT00896480	Melanoma			
			Ph II	NCT00942162	Melanoma			
Immatics Biotech (private)	IMA901		Ph II	NCT00523159	Renal	Allogeneic	Peptide	Peptides with multiple antigens from Class I/II TUMAPs
	IMA910		Ph I/II	NCT00785122	Colorectal			
Immunocellular Therap (IMUC.OB)	ICT-107		Ph I	n/a	Glioblastoma	Autologous	DC	DCs with IM2, Her-2/neu, gp-100, MAGE-1, TRP-2 and IL13Ra2 antigens.
Immutep S.A.	IMP321		Ph I	NCT00349934	Breast	Allogeneic	Peptide	Soluble form of LAG-3 that binds, with high affinity, to MHC class II molecules expressed by dendritic cells and monocytes causing a robust T cell response
			Ph I	NCT00732082	Pancreatic			
			Ph I/II	NCT00365937	Melanoma			
Inovio Biomedical (INO)	VGX™-3100	-	Ph I	NCT00685412	Cervical	Allogeneic	Gene Transfer	DNA based vaccines based on commonly expressed antigens and delivered through electroporation
	V934	Merck	Ph I	NCT00753415	Multiple			
	V930	-	Ph I	NCT00647114	Multiple			
	PSMA27	-	Ph I/II	n/a	Prostate			
Juvaris (private)	JVRS-100		Ph I	NCT00860522	Leukemia	Immune Stimulation	Adjuvant	Induction of innate immunity via stimulation of both toll-like receptors and cytosolic interferon induction pathways

Company	Product(s)	Partner	Stage	ClinicalTrials.gov Identifier	Disease	Category	Strategy	Description
MannKind Corp. (MNKD)	MKC1106-PP		Ph II Ph I Ph I	NCT01026051 NCT00688090 NCT00423254	Melanoma Melanoma Multiple	Allogeneic	Gene Transfer	Peptide with a DNA vector delivering two synthetic peptides (PRAME and PSMA)
MolMed S.p.A. (Milan:MLM)	M3TK		Ph I/II	n/a*	Melanoma	Autologous	Cellular	T lymphocytes, genetically engineered <i>ex vivo</i> to express the tumor antigen MAGE-3 and acting as antigen carriers for efficient loading of DCs
Northwest Biotherapeutics Inc. (NWBO.OB)	DCVax		Ph II Ph III Ph I	NCT00045968 NCT00043212* NCT00683241	Glioblastoma Prostate Ovarian	Autologous	DC	DCs extracted from the patient and loaded with tumor lysate/antigens
NovaRx Corp. (private)	Lucanix		Ph III	NCT00676507	Lung	Allogeneic	Cellular	NSCLC cell line with siRNA against TGF- $\beta$
Oncothyreon Inc. (ONTY)	Stimuvax	Merck Serono	Ph II Ph III Ph III	NCT01094548** NCT00925548** NCT00409188**	Myeloma Breast Lung	Allogeneic	Peptide	Incorporates a 25-amino acid sequence of the cancer-associated marker MUC-1 in a liposomal formulation
Oxford BioMedica (OXB.L)	TroVax		Ph III Ph II	NCT00397345 NCT00521274*	Renal Cell Prostate	Allogeneic	Gene Transfer	5T4-specific therapeutic vaccine delivered via vaccinia virus Ankara
Prima Biomed (PRR.AX)	CVac		Ph II	NCT01068509	Ovarian	Autologous	DC	DCs primed with MUC-1 and mannan adjuvant

Company	Product(s)	Partner	Stage	ClinicalTrials.gov Identifier	Disease	Category	Strategy	Description
Progenics Pharmaceuticals (PGNX)	rsPSMA PSMAvrp		Ph I Ph I	NCT00705835 n/a	Prostate	Allogeneic	Gene Transfer	PSMA-VRP vaccine expressing the extracellular domain of PSM; based on the platform alphavirus replicon vector
Provectus Pharmaceuticals Inc. (PVCT.OB)	PV-10 (rose bengal)		Ph II	NCT00521053	Melanoma	Other	Other	Intralesional PV-10 is selectively toxic to cancer cells with bystander response in untreated lesions
Quantum Immunologics (private)	OFA		Ph I Ph I/II	NCT00715832 NCT00879489	Breast	Autologous	DC	DCs with oncofetal antigen/immature laminin receptor protein (OFA/iLRP)
Transgene S.A. (TNG.NX)	TG4010	Novartis	Ph II/III	NCT00415818	Lung	Allogeneic	Gene Transfer	Recombinant vaccinia virus expressing MUC-1
Vaccinogen, Inc	OncoVAX		Ph III	n/a	Colon	Autologous	Cellular	metabolically active, irradiated, non-tumorigenic cells with BCG as an adjuvant
VaxOnco Inc. (private)	Onyvax-P		Ph II	NCT00514072	Prostate	Allogeneic	Cellular	Combination of inactivated cell lines that are representative of different stages of the disease
Vical Inc. (VICL)	Allovectin-7	AnGes MG Inc.	Ph III	NCT00395070	Melanoma	Allogeneic	Gene Transfer	Plasmid/lipid complex containing the DNA sequences encoding HLA-B7 and $\beta$ 2 microglobulin, and directly injected into tumor lesion

\*Study terminated according to ClinicalTrials.gov    \*\*Study suspended according to ClinicalTrials.gov

## APPENDIX C: COMPANY PROFILES

### ADVAXIS, INC. (ADXS.OB)

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#### MANAGEMENT

- Thomas A. Moore, Chairman of the Board of Directors/CEO
- John Rothman, Ph.D., EVP Clinical Development
- Mark Rosenblum, Chief Financial Officer
- Conrad F. Mir, Executive Director of Business Development

#### DESCRIPTION

Advaxis, Inc. is a biotechnology company that uses a bioengineered bacterium, *Listeria monocytogenes* to activate the immune system to treat cancer, infectious disease or allergic syndromes. Based upon more than 20 years of discovery by Yvonne Paterson, Ph.D., Professor of Microbiology at the University of Pennsylvania, it has been found that this unique microbe is capable of stimulating numerous aspects of the immune system simultaneously; including, strongly stimulating innate immunity and both arms of the cellular adaptive immune response, stimulating non-classical immune mechanisms in the blood and bone marrow, and altering tumor microenvironments to allow the immune response to work.

This unique approach has resulted in extremely effective agents for the treatment of existing cancers and other diseases. Unlike other therapeutic approaches, in pre-clinical research Advaxis' *Listeria* technology has been able to consistently demonstrate complete therapeutic responses resulting in complete tumor regression. Preliminary results in humans have shown this technology to be safe, and the therapeutic outcomes are very encouraging.

Advaxis is developing ADXS11-001, a live *Listeria monocytogenes* vaccine directed against the tumor-associated antigen HPV-16-E7 that treats human papilloma virus (HPV) related tumors. Unlike marketed prophylactic vaccines that require treatment prior to exposure to the virus, ADXS11-001 treats patients who have already developed cancer as a result of HPV infection.



Chart courtesy of StockCharts.com

## ALPHAVAX, INC. (PRIVATE)

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### MANAGEMENT

- Tim Gupton, CPA, CFO
- Steve Udem, M.D., Ph.D., Acting Chief Scientific Officer
- Janice Kimpel, Ph.D., VP Business Development
- Robert Olmsted, Ph.D., VP Research
- Andrew Graham, M.S., VP Development & Technical Operations
- Lynn G. Baird, Ph.D., VP Regulatory, Quality and Clinical Operations

### DESCRIPTION

AlphaVax uses a specialized viral vector system to make alphavirus replicon vaccines called alphavaccines. Since 1998, the company has raised more than \$154 million, with ~75% coming from corporate partner and grant funding. AlphaVax is the first company to advance an alphavirus-vectored vaccine to the clinical stage of development.

This Alphavaccine Platform System is genetically derived from a modified alphavirus. The company re-engineers the virus, substituting a gene from an infectious disease or cancerous cell for a portion of the original viral genome. The re-engineered alphavaccine particles express the substituted gene (or genes) rather than producing more virus particles, transforming the original virus into a highly effective vaccine system.

In September 2001, AlphaVax has granted an exclusive license to Progenics Pharmaceuticals, Inc. to develop an alphavaccine product expressing PSMA (prostate specific membrane antigen), an antigen that is over-expressed in prostate and other cancers. In November 2008, Progenics announced plans to initiate a 29-week, Phase I study.

Researchers at the Duke Comprehensive Cancer Center and AlphaVax are co-investigators on two cancer vaccine development grants from the National Cancer Institute (NCI) and the Department of Defense (DoD), Breast Cancer Research Program. The colon cancer vaccine is currently being evaluated in a phase I/II clinical trial funded by the NCI and a breast cancer vaccine was scheduled to enter a phase I/II clinical trial in 4Q 2009 that is funded by the DoD.

## ANTIGENICS, INC. (AGEN)

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Fax: 781-674-4200  
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### MANAGEMENT

- Garo H. Armen, PhD, Chairman and Chief Executive Officer
- John Cerio, Vice President, Human Resources
- Stephen Monks, PhD, Vice President, Manufacturing and PAT
- Shalini Sharp, Chief Financial Officer and Vice President
- Sunny Uberoi, Vice President, Corporate Communications
- Karen Higgins Valentine, Vice President & General Counsel
- Kerry A. Wentworth, Vice President, Regulatory Affairs and Clinical Operations

### DESCRIPTION

Antigenics is an emerging biopharmaceutical company developing treatments for cancers and infectious diseases. The company's product portfolio includes its late-stage development candidate Oncophage® (vitespen; heat shock protein technology), a patient-specific therapeutic cancer vaccine that has recently been approved in Russia for use as an adjuvant treatment for renal cell carcinoma (RCC) in patients at intermediate risk of disease recurrence; and the QS-21 Stimulon® Adjuvant, a vaccine adjuvant being evaluated by Antigenics' corporate licensees in several Phase II and III clinical trials.

Outside Russia, Oncophage is an investigational patient-specific vaccine designed to treat cancer with the intent of minimizing side effects. Currently being evaluated in clinical trials, treatment with Oncophage is designed to target only cancerous cells — not healthy normal cells. As a result, Oncophage is designed to limit the toxicities associated with traditional broad-acting cancer treatments. Oncophage is currently being tested in Phase II trials for glioblastoma patients.

Antigenics is also developing QS-21, one of the world's most widely studied immune adjuvants. This investigational adjuvant is being tested in several advanced clinical vaccine programs in partnership with leading pharmaceutical companies.



Chart courtesy of StockCharts.com

## APTHERA, INC. (PRIVATE)

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### MANAGEMENT

- William E. Gannon, M.D., Chief Medical Officer
- Robert E. Kennedy, Chief Financial Officer
- Mark W. Schwartz, Ph.D., President & Chief Executive Officer
- Joseph Sinkule, Pharm.D., Chief Scientific Officer
- Brent F. G. Treiger, M.D., V.P. - Clinical Affairs

### DESCRIPTION

Apthera, Inc. was founded in July, 2005 to develop and commercialize a pipeline of peptide-based immunotherapies for the adjuvant treatment of HER2-positive cancers. Currently, the Company has products in clinical trials aimed at reducing disease recurrence rates for breast and prostate cancers. Apthera licensed its core intellectual property from The University of Texas M. D. Anderson Cancer Center (MDACC) in Houston, TX, and The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (HJF) in Rockville, MD.

Apthera recently announced positive Phase I/II clinical trial results for its lead cancer immunotherapy product, NeuVax™ for the treatment of breast cancer. NeuVax™ is a peptide-based immunotherapy that recruits the immune system to fight cancer and activates "Killer T-cells" to target tumors. NeuVax™ specifically targets cancer while leaving normal, healthy tissues unharmed. The key to NeuVax™ is a small peptide called E75 that is derived from HER2/neu, a protein expressed by tumors.

Planning is underway for a large, international, pivotal Phase III clinical trial of NeuVax™ for the treatment of early-stage (node-positive) HER2-positive breast cancer. Apthera intends to obtain regulatory approval of NeuVax™ for the treatment of breast cancer in both the U.S. and international markets.

## ARGOS THERAPEUTICS (PRIVATE)

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Website: <http://www.argosterapeutics.com>

### MANAGEMENT

- Jeffrey D. Abbey, M.B.A., J.D., President, Chief Executive Officer
- Frederick M. Miesowicz, Ph.D., Chief Operating Officer
- Charles A. Nicolette, Ph.D., Chief Scientific Officer, Vice President, Research and Development

### DESCRIPTION

Argos Therapeutics is an immunotherapy company developing new treatments for cancer, infectious and autoimmune diseases, and transplantation rejection. The company has generated multiple platform technologies and a diverse pipeline of products based on its expertise in the biology of dendritic cells – the master switch that turns the immune system on or off. Argos has clinical trial programs in cancer and human immunodeficiency virus (HIV) and has an ongoing co-development and commercialization alliance Kyowa HakkoKirin Brewery Co., Ltd.

Arcelis™, Argos' core technology for creating personalized immunotherapies, is designed to better harness the power of dendritic cells to treat cancer, HIV and other infectious diseases by loading these cells with a patient's own tumor or viral RNA. This process triggers an immune response that is 100% relevant for that particular patient, enabling completely personalized immunotherapy.

Argos is currently conducting two phase 2 clinical trials of its Arcelis™ immunotherapy in RCC, testing the therapy as both a single-agent and also in combination with sunitinib. Argos has completed an initial Phase 1/2 study of the immunotherapy in RCC. The trial successfully demonstrated that the immunotherapy was well-tolerated (no drug related serious adverse events) and the commercial feasibility of processing the product at a central manufacturing facility with delivery to multiple clinical sites. In addition, disease progression and overall median survival data from the trial were encouraging.

## AVAX TECHNOLOGIES, INC. (AVXT.PK)

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### MANAGEMENT

- John K. A. Prendergast, Ph.D., Chairman and Chief Executive Officer
- Henry E. Schea III, Director of Global Quality and Regulatory Affairs

### DESCRIPTION

AVAX Technologies, Inc. is an internationally integrated biotechnology company focused on developing and commercializing its Autologous Cell (AC) Vaccine<sup>®</sup> technology for the treatment of cancer. The AC Vaccine Technology is an immunotherapeutic treatment that educates the patient's immune system to recognize cancer cells as foreign through the process of haptization. Haptization is a re-education of the immune system through a chemical modification of antigens on the cancer cell which allows for the development of an immune response to cancer cells that were previously ignored by the immune system. To produce AVAX's AC Vaccine cancer cells are obtained from tumors excised during routine surgery. These cells are then treated with the hapten dinitrophenyl (DNP). Injection of the DNP-modified vaccine induces an immune response against native cancer cells in the patient's body, and, under the best of circumstances, kills them or controls their growth.

MVax<sup>®</sup> for the Treatment of Melanoma: AVAX has launched an international Phase III registration trial comparing MVax<sup>®</sup> plus low dose Interleukin-2 versus placebo vaccine plus low dose Interleukin-2 in patients with stage IV melanoma. The study, which initiated enrollment in November 2007, is recruiting centers in the U.S., Europe and Israel. The study is the subject of a Special Protocol Assessment Agreement (SPA) with the U.S. FDA.

OVax<sup>®</sup> for the Treatment of Ovarian Cancer: AVAX has executed a collaboration and production agreement with Cancer Treatment Centers of America, Inc. (CTCA) for AVAX's OVax, a vaccine therapeutic for the treatment of ovarian cancer and for the production of CTCA's activated natural killer (NK) cell technology for the treatment of various human cancers. AVAX is conducting a Phase I/II trial through the CTCA for the treatment of stage III & IV ovarian cancer patients who have relapsed following chemotherapy.



Chart courtesy of StockCharts.com

## BAVARIAN NORDIC A/S (BAVA.CO)

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### MANAGEMENT

- Anders Hedegaard, President & CEO
- Steen Vangsgaard, EVP, Commercial Affairs
- Paul Chaplin, EVP, Research and Development & CSO
- Ole Larsen, EVP, CFO
- Anders Gram, EVP, Technical Operations
- Reiner Laus, EVP, CEO of BN ImmunoTherapeutics
- Morten Max Rasmussen, EVP, Transactions, Legal and IPR

### DESCRIPTION

Bavarian Nordic A/S is a leading industrial biotechnology company developing and producing novel vaccines for the treatment and prevention of life-threatening diseases with a large unmet medical need. The company's pipeline is focused in the three areas; cancer, biodefense and infectious diseases, and includes seven development programs.

Bavarian Nordic is currently pursuing the development of active immunotherapy targeting two of the major cancers; breast and prostate cancer. Viral vector-based vaccines, like MVA-BN®, offer the advantage that the virus will induce both a strong humoral and a cellular immune response.

PROSTVAC™, which was acquired through a collaboration with the National Cancer Institute, is not based on MVA-BN®, but uses two recombinant Poxviral vectors (Vaccinia and fowl pox).

Encouraging results from Phase II studies with PROSTVAC™ demonstrate a clear survival benefit along with a very favorable safety profile when compared to existing treatment options (chemotherapy) in patients suffering from advanced prostate cancer. Confirmatory Phase III studies are expected to form the basis for the approval of the vaccine, thus fulfilling a large unmet medical need.

## BIOANTE PHARMACEUTICALS, INC. (BPAX)

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### MANAGEMENT

- Stephen M. Simes, President and Chief Executive Officer
- Phillip B. Donenberg, CPA, Chief Financial Officer, Treasurer and Secretary
- Bill Milling, Controller and Senior Director of Operations
- Michael C. Snabes, Vice President of Clinical Development

### DESCRIPTION

BioSante is developing its GVAX cancer vaccines, which the company acquired through a merger with Cell Genesys in 2009. GVAX immunotherapy is comprised of cancer cell lines that are genetically modified to secrete granulocyte-macrophage colony stimulating factor (GM-CSF), an immunostimulatory cytokine, and then irradiated for safety. GVAX immunotherapy is designed to be administered through intradermal injections on an outpatient basis. GVAX has been studied in Phase III trials in prostate cancer and is currently the subject of Phase II trials in acute myeloid leukemia (AML) and pancreatic cancer.

In a recent paper published in the peer-reviewed journal *Blood*<sup>62</sup>, clinical investigators, led by investigators at Johns Hopkins University, reported on the results of a Phase II study of GVAX in combination with autologous stem cell transplantation for the treatment of AML. Fifty-four subjects were enrolled; 46 (85%) achieved a complete remission, and 28 (52%) received the pre-transplantation immunotherapy. For all patients who achieved complete remission, the 3-year relapse-free survival (RFS) rate was 47.4% and overall survival was 57.4%. For the 28 immunotherapy-treated patients, the RFS and overall survival rates were 61.8% and 73.4%, respectively. Post-treatment induction of delayed-type hypersensitivity reactions to autologous leukemia cells was associated with longer 3-year RFS rate (100% vs 48%). Minimal residual disease was monitored by quantitative analysis of Wilms tumor-1 (WT1), a leukemia-associated gene. A decrease in WT1 transcripts in blood was noted in 69% of patients after the first immunotherapy dose and was also associated with longer 3-year RFS (61% vs 0%). In conclusion, immunotherapy in combination with primed lymphocytes and autologous stem cell transplantation shows encouraging signals of potential activity in acute myeloid leukemia.



Chart courtesy of StockCharts.com

## BIOVEST INTERNATIONAL, INC. (BVTI.PK)

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### MANAGEMENT

- Francis E. O'Donnell, Jr. MD, Chairman
- Samuel S. Duffey, Esq., President and General Counsel
- Mark Hirschel, Ph.D., Chief Scientific Officer
- Alan Pearce, Chief Financial Officer
- David D. Moser, Corporate Secretary

### DESCRIPTION

Biovest International, Inc., a majority-owned subsidiary of Accentia Biopharmaceuticals, Inc. (ABPIQ.PK), is an emerging leader in the field of personalized immunotherapies targeting life-threatening cancers of the blood system. Developed in collaboration with the National Cancer Institute, BiovaxID<sup>®</sup> is a patient-specific, anti-lymphoma cancer vaccine, demonstrating statistically significant Phase III clinical benefit by prolonging disease-free survival in patients suffering from indolent follicular non-Hodgkin's lymphoma. BiovaxID<sup>®</sup> has been granted Orphan Drug Designation by both the U.S. FDA and the European EMEA.

As BiovaxID<sup>®</sup> is individually manufactured from a tissue biopsy obtained from a patient's own tumor, a patient must undergo a lymph node biopsy prior to receiving chemotherapy/monoclonal antibody therapy. Those cells collected by biopsy will then undergo a preparation process performed by Biovest with the resulting vaccine material then preserved until manufacture of the final vaccine is prescribed by the patient's physician. The vaccine is typically administered approximately 6 months following the end of chemotherapy, and consists of five BiovaxID<sup>®</sup> vaccinations, subcutaneously injected, over a 6 month period (months 1,2,3,4 and 6). As an adjuvant therapy, at each vaccination cycle, patients will also receive four daily injections of an immune stimulating agent, GM-CSF. At the physician's option, a periodic vaccine booster maintenance regimen may also be prescribed.



Charts courtesy of StockCharts.com

## BRISTOL-MYERS SQUIBB (BMY)

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### MANAGEMENT

- James M. Cornelius, Chairman & CEO
- Lamberto Andreotti, President and Chief Operating Officer, and CEO-designate
- Sandra Leung, Senior Vice President, General Counsel & Corporate Secretary
- Elliott Sigal, Executive Vice President, Chief Scientific Officer & President, R&D

### DESCRIPTION

Bristol-Myers Squibb is developing ipilimumab (also known as MDX-010, or MDX-101), which is currently being studied with or without MDX-1379, a vaccine consisting of two gp100 melanoma peptides, in a Phase III trial. The peptides are recognized by cytotoxic T cells in melanoma patients that are positive for HLA-A2, representing approximately half of the population.

Ipilimumab is a human monoclonal antibody that binds to cytotoxic T lymphocyte-associated antigen (CTLA)-4, a protein expressed on T-cells that is believed to play a critical role in regulating natural immune responses through the suppression of T cell activation and proliferation. The absence or presence of CTLA-4 on the cell surface can augment or suppress the immune system's T-cell response in fighting disease. Ipilimumab is designed to block the activity of CTLA-4, thereby sustaining an active T cell response in its attack on cancer cells. Ipilimumab is currently being developed by Bristol-Myers Squibb and is undergoing late-stage clinical trials for the treatment of metastatic melanoma, lung cancer, and prostate cancer.

Upcoming milestones expected in 2010 include the presentation of Phase III data from a vaccine combination/monotherapy study in pretreated patients at ASCO 2010, data from first-line survival study in combination with dacarbazine (DTIC), and potential US and EU regulatory submissions.



Charts courtesy of StockCharts.com

## CEL-SCI CORPORATION (CVM)

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### MANAGEMENT

- Maximilian de Clara, Director and President
- Geert R. Kersten, Director and Chief Executive Officer
- Patricia B. Pritchep, Senior VP of Operations
- Eyal Talor, Ph.D., Chief Scientific Officer
- Daniel Zimmerman, Ph.D., Senior VP of Cellular Immunology
- John Cipriano, Senior VP of Regulatory Affairs

### DESCRIPTION

CEL-SCI Corporation is developing Multikine<sup>®</sup>, a patented defined mixture of naturally derived cytokines that the company describes as a new class of drugs called "Immune SIMULATORS." Immune SIMULATORS simulate the way our natural immune system acts in defending us against cancer. As opposed to other immunotherapies which are designed to target a single or limited number of specific antigens or molecules, Immune SIMULATORS are multi-targeted.

According to the company, Multikine<sup>®</sup> is also the first immunotherapeutic agent being developed as a first-line standard of care treatment for cancer. It is administered prior to any other cancer therapy because that is the period when the anti-tumor immune response can still be fully activated. Once the patient has advanced disease, or had surgery or has received radiation and/or chemotherapy, the immune system is severely weakened and is less able to mount an effective anti-tumor immune response. Other immunotherapies are administered after the patient has received surgery, chemotherapy and/or radiation therapy, which can limit their effectiveness.

In Phase II clinical trials Multikine<sup>®</sup> was shown to be safe and well-tolerated, and to improve patients' overall survival by 33% over what can be attained with standard treatment alone (without the addition of Multikine<sup>®</sup> therapy) at a median of three and a half years following surgery. The Company is planning a Phase III clinical trial in the neoadjuvant therapy of patients having squamous cell carcinoma (cancer) of the head and neck.



Charts courtesy of StockCharts.com

## CELLEX THERAPEUTICS, INC. (CLDX)

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Fax: 781-433-0262  
Website: <http://www.celldextherapeutics.com>

### MANAGEMENT

- Anthony S. Marucci, Founder, President and Chief Executive Officer
- Avery W. ("Chip") Catlin, Senior Vice President and Chief Financial Officer
- Tibor Keler, Ph.D., Founder, Senior Vice President and Chief Scientific Officer
- Thomas Davis, M.D., Senior Vice President and Chief Medical Officer

### DESCRIPTION

Celldex Therapeutics is the first antibody-based combination immunotherapy company. The company has a pipeline of drug candidates in development for the treatment of cancer and other difficult-to-treat diseases based on its antibody focused Precision Targeted Immunotherapy Platform (PTI), a complementary portfolio of monoclonal antibodies, antibody-targeted vaccines and immunomodulators.

The company's lead clinical development program, CDX-110, is an immunotherapy that targets the tumor specific molecule called EGFRvIII, a functional variant of the epidermal growth factor receptor (EGFR), a protein that has been well validated as a target for cancer therapy. While many different epithelial tumors express this antigen, glioblastoma multiforme (GBM) has a particularly dire prognosis and is the Company's primary indication at this time.

In collaboration with its corporate partner, Pfizer, Inc., Celldex is currently performing a Phase II study (the "ACT III" study) of CDX-110 in approximately 60 patients with newly diagnosed GBM. Objectives of the study are to investigate the anticancer activity, impact on survival, and safety of CDX-110 when administered during a 12 month course of maintenance temozolomide chemotherapy and then continuing until disease progression.

The company's second product candidate, CDX-1307, is in Phase I development for the treatment of colorectal, pancreatic, bladder, ovarian and breast cancers. CDX-1307 targets the beta chain of human chorionic gonadotropin, known as hCG- $\beta$ , an antigen often found in these and other types of tumors. Celldex is planning the initiation of a Phase II study in patients with newly diagnosed bladder cancer in the first quarter of 2010.



Charts courtesy of StockCharts.com

## CYTOS BIOTECHNOLOGY AG (CYTN.SW)

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Website: <http://www.cytos.com>

### MANAGEMENT

- Wolfgang A. Renner, Ph.D., Delegate of the Board of Directors and Chief Executive Officer
- Martin F. Bachmann, Ph.D., Executive Vice President and Chief Scientific Officer
- Mark Dyer, Ph.D., Executive Vice President Business Development and Strategy
- Frank Hennecke, Ph.D., Executive Vice President Product Development
- Philipp Müller, M.D., Executive Vice President Clinical Development
- Jakob Schlapbach, Lic. rer. pol. and MBA (INSEAD), Executive Vice President and Chief Financial Officer
- Hans Stocker, Ph.D., Executive Vice President Regulatory Affairs

### DESCRIPTION

Cytos Biotechnology Ltd is a public Swiss biotechnology company engaged in the discovery, development and commercialization of a novel class of biopharmaceutical products known as Immunodrugs™. Six vaccine candidates are being developed both in-house as well as in partnership with leading pharmaceutical companies (Novartis, Pfizer, Pfizer Animal Health).

CYT004-MelQbG10 is the company's therapeutic vaccine in Phase IIa development for the treatment of malignant melanoma. It is based on Cytos' second Immunodrug™ platform, which applies immunostimulatory DNA sequences to induce targeted T cell responses. CYT004-MelQbG10 consists of a modified fragment of the Melan-A protein coupled to the Immunodrug™ carrier QbG10. QbG10 itself encompasses the virus-like particle Qb, which has been filled with the immunostimulatory DNA sequence G10. G10 is a synthetically produced stretch of DNA originally derived from bacteria. This DNA sequence is recognized by so called toll-like receptors, which sound an "alarm signal" to the immune system and this way provide the inflammatory context necessary to promote T cell activation. Melan-A is a melanocyte-differentiation antigen and, although its exact function is not yet known, it has been found to be over-expressed in melanoma cells.

## DENDREON CORPORATION (DNDN)

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<http://www.dendreon.com>

### MANAGEMENT

- Mitchell H. Gold, M.D., President and Chief Executive Officer and Director
- Hans E. Bishop, Executive Vice President and Chief Operating Officer
- Mark W. Frohlich, M.D., Senior Vice President, Clinical Affairs and Chief Medical Officer
- Richard F. Hamm, Jr., Senior Vice President, Corporate Development, General Counsel, and Secretary
- Gregory T. Schiffman, Senior Vice President and Chief Financial Officer
- David L. Urdal, Ph.D., Senior Vice President, Chief Scientific Officer and Director

### DESCRIPTION

Dendreon Corporation is focused on the discovery, development and commercialization of novel active cellular immunotherapy and small molecule products to treat a wide range of cancers. Dendreon's most advanced product candidate is sipuleucel-T, an active cellular immunotherapy (ACI) that has been studied in Phase 3 trials for the treatment of metastatic, castrate-resistant (also known as androgen-independent or hormone-refractory) prostate cancer. Sipuleucel-T, an investigational ACI, has completed two Phase 1 clinical trials for the potential treatment of patients with breast, ovarian and colorectal solid tumors expressing HER2/neu.

Sipuleucel-T contains mature, autologous antigen- presenting cells (APCs). Approximately two days before each scheduled infusion, APCs are obtained from the patient via a standard blood collection process that isolates a patient's white blood cells called leukapheresis. The patient's APCs are then transported to a Dendreon manufacturing facility where they are co-cultured with a recombinant fusion protein containing prostatic acid phosphatase (PAP).

The activated, antigen-loaded APCs (now sipuleucel-T) are then delivered to the physician's office (infusion site) for infusion into the patient. Sipuleucel-T is then infused into the patient, where it can potentially stimulate a T cell response against prostate cancer cells. The process is performed three times over the course of a four-week period, upon which treatment is completed.



Charts courtesy of StockCharts.com

## GENEREX BIOTECHNOLOGY (GNBT)

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Website: <http://www.generex.com>

### MANAGEMENT

- Anna E. Gluskin, Chairman, President, CEO
- Rose C. Perri, Chief Financial Officer, COO, Treasurer, Sec., Director
- Mark Fletcher, Executive Vice President, General Counsel
- Dr. Eric von Hofe, Ph.D., Vice-President of Generex and President of Antigen Express
- William D. Abajian, Senior Executive Advisor, Global Strategic Alliances & Business Development
- Dr. Gerald Bernstein, M.D., Vice President, Medical Affairs, Director

### DESCRIPTION

Generex is engaged in the research, development, and commercialization of drug delivery systems and technologies. The company's Antigen Express technology focuses on modulating immune responses mediated by T helper (Th) cells, a class of lymphocytes that plays a multifaceted role in the immune system, both enhancing and suppressing immune responses.

The vaccines under development utilize specific fragments of known pathogenic agents or markers of disease modified by proprietary means to increase their immune-stimulatory activity. The company's most advanced compound (AE37) has been shown to be safe, well tolerated and to generate a good immunological response in breast cancer patients in a Phase I clinical trial. This immunotherapeutic vaccine is currently being examined in a randomized, controlled Phase II study designed to examine efficacy in breast cancer patients as well as in a new Phase I study in prostate cancer patients.



Charts courtesy of StockCharts.com

## GENITOPE CORPORATION (GTOP.PK)

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Website: <http://www.genitope.com>

### MANAGEMENT

- Dan W. Denney, Jr., Ph.D., Chief Executive Officer and interim Chief Financial Officer

### DESCRIPTION

Genitope Corporation has suspended development of its lead product candidate, MyVax<sup>®</sup> Personalized Immunotherapy (previously referred to as GTOP-99) and is continuing to evaluate the data from its pivotal Phase III clinical trial of MyVax<sup>®</sup> personalized immunotherapy in previously untreated follicular B-cell non-Hodgkin's lymphoma patients and related data, with the goal of obtaining value for MyVax<sup>®</sup> personalized immunotherapy, but the outcome of this evaluation and the Company's ability to obtain value remains highly uncertain.

Genitope was founded in 1996 by Dan W. Denney, Jr., Ph.D., after he developed the company's Hi-GET<sup>®</sup> technology, which is designed to rapidly and efficiently produce immunotherapies. In April 2008, the company retained an investment bank to act as its financial advisor to provide financing and strategic advisory services to the company. In connection with this engagement, representatives of the investment bank contacted a wide range of third parties seeking a possible investment in the company or with respect to the company's assets, or a partnership, licensing or acquisition transaction with the company. To date, no third party has proposed terms for such a transaction. Accordingly, irrespective of the outcome of the company's continuing evaluation with respect to its MyVax<sup>®</sup> personalized immunotherapy program, the Company anticipates that it will seek protection under the federal bankruptcy laws or liquidate its assets and dissolve the corporation.



Charts courtesy of StockCharts.com

## GERON CORPORATION (GERN)

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### MANAGEMENT

- Thomas B. Okarma, Ph.D., M.D., President, Chief Executive Officer and Director
- David L. Greenwood, Executive Vice President, Chief Financial Officer, Treasurer and Secretary
- Stephen M. Kelsey, M.D., F.R.C.P., F.R.C.Path., Executive Vice President, Chief Medical Officer, Oncology
- David J. Earp, Ph.D., J.D., Chief Patent Counsel and Senior Vice President, Business Development
- Melissa A. Kelly Behrs, Senior Vice President, Therapeutic Development, Oncology
- Jane S. Lebkowski, Ph.D., Senior Vice President, Chief Scientific Officer, Regenerative Medicine
- Katharine E. Spink, Ph.D., Vice President Operations, Regenerative Medicine

### DESCRIPTION

Geron is developing first-in-class biopharmaceuticals for the treatment of cancer and chronic degenerative diseases, including spinal cord injury, heart failure and diabetes. GRNVAC1 is the company's an autologous product consisting of mature dendritic cells pulsed with RNA for the protein component of human telomerase (hTERT) and a portion of a lysosomal targeting signal (LAMP). A Phase II Geron-sponsored clinical study of GRNVAC1 is being conducted at six U.S. medical centers using a prime-boost vaccination protocol in patients with acute myelogenous leukemia (AML) in complete clinical remission and examines the safety and feasibility of a prime-boost vaccination regimen to extend the duration of telomerase immunity. This trial completed patient enrollment in December 2009.



Charts courtesy of StockCharts.com

## GLAXOSMITHKLINE PLC (GSK)

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Website: <http://www.gsk.com>

### MANAGEMENT

- Andrew Witty, Chief Executive Officer
- Julian Heslop, Chief Financial Officer

### DESCRIPTION

GlaxoSmithKline's antigen-specific cancer immunotherapeutics (ASCIs) represent a novel class of medicines designed to train the immune system to recognize and eliminate cancer cells in a highly specific manner. These novel cancer immunotherapeutics combine tumor antigens, delivered as purified recombinant proteins, and GSK's proprietary Adjuvant Systems which are specific combinations of immunostimulating compounds selected to increase the anti-tumor immune response. ASCIs will be investigated to support their use to reduce the risk of tumor recurrence following surgery, or to impact tumor growth in an early metastatic setting.

MAGE-A3 is a tumor-specific antigen that is expressed in a large variety of cancers, including melanoma, non-small cell lung cancer (NSCLC), head and neck cancer, bladder cancer, with no expression in normal cells. Expression of the MAGE-A3 gene has been observed in testicular cells but without antigen presentation capabilities.

MAGE-A3 protein has been in-licensed by GSK from the Ludwig Institute for Cancer Research, the largest international academic institute dedicated to understanding and controlling cancer. Encouraging results from the Phase II NSCLC study have led to a Phase III safety and efficacy trial in MAGE-A3-positive NSCLC patients (stage IB, II and IIIA) who have undergone complete surgical resection.



Charts courtesy of StockCharts.com

## IMMATICS BIOTECHNOLOGIES GMBH (PRIVATE)

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Website: <http://www.immatics.net>

### MANAGEMENT

- Paul Higham, B.Sc. Hons. (Managing Director, Chief Executive Officer)
- Carsten Reinhardt, M.D. Ph.D. (Managing Director, Chief Medical Officer)
- Harpreet Singh, Ph.D. (Managing Director, Chief Scientific Officer, Co-Founder)

### DESCRIPTION

Immatics Biotechnologies discovers and develops tumor-associated peptides (TUMAPs) for the immunotherapy of cancer. On the basis of proprietary drug discovery technologies, the company identifies HLA-binding TUMAPs with highest sensitivity directly from primary human tumor tissue samples. From thousands of identified TUMAPs the most suitable ones are selected and combined to a single multi-peptide product to form a therapeutic cancer vaccine. The goal is to provoke a number of specific T-cell responses which finally result in the destruction of tumor cells presenting the applied TUMAPs.

There are two classes of TUMAPs:

- Class I: short peptides (8 to 12 amino acids), intended to activate cytotoxic T cells
- Class II: long peptides (more than 15 amino acids), intended to activate T helper cells

The first steps of TUMAP discovery to the beginning of clinical testing (Phase I) requires 24 months or less. Immatics' most advanced product (IMA901) entered a Europe-wide multi-center Phase II clinical trial in 2007 for kidney cancer and a second product targeting colorectal cancer (IMA910) has recently entered a large Phase I/II clinical trial. The company also has preclinical leads as well as active earlier programs in several other tumor types.

## IMMUNOCELLULAR THERAPEUTICS, LTD. (IMUC.OB)

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Woodland Hills, CA 91367  
Phone: 818-992-2907  
Website: <http://imuc.com>

### MANAGEMENT

- Manish Singh, Ph.D., MBA, President and Chief Executive Officer
- John S. Yu, M.D., Chief Scientific Officer and Chairman of the Board
- C. Kirk Peacock, Chief Financial Officer
- James G. Bender, Ph.D., M.P.H., Vice President, Clinical Development

### DESCRIPTION

ImmunoCellular Therapeutics recently completed a Phase I trial of its lead product candidate, ICT-107, a dendritic cell-based vaccine targeting multiple tumor associated antigens for glioblastoma. The trial enrolled 19 patients and was conducted at Cedars-Sinai Medical Center. It was reported in November 2008 that of the 19 patients enrolled, 17 patients were still alive with eight patients surviving at least one year after the surgery that preceded their vaccine treatment. Ten patients were evaluated for immune responses, and five of them had a significant immune response to at least one tumor-associated antigen. Patients demonstrating an immune response are exhibiting a trend toward longer overall survival. The Company is planning to initiate a multicenter phase II study in the second half of 2010.

The Company's "off the shelf" therapeutic vaccine product candidate (ICT-121) targeting cancer stem cells for multiple cancer indications is targeted by IMUC to enter clinical trials for glioblastoma during the second half of 2010. ICT-121 consists of a peptide to stimulate a Cytotoxic T-Lymphocyte (CTL) response to CD-133, which is generally overexpressed on the cancer stem cells. It is designed as an off-the-shelf vaccine which may be applicable to multiple types of cancers overexpressing CD-133.



Charts courtesy of StockCharts.com

## IMMUTEP S.A. (PRIVATE)

Faculté de Pharmacie  
5 rue Jean-Baptiste Clément  
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Website: <http://www.immutep.com>

### MANAGEMENT

- John B. Hawken, President and CEO
- Frédéric Triebel, Scientific and Medical Director

### DESCRIPTION

Immutep is developing two complementary types of therapeutic proteins based on newly-discovered pathways involved in the Lymphocyte Activation Gene-3 (LAG-3) immune control mechanism, which plays a vital role in the regulation of the immune system. The lead product, ImmuFact® IMP321, is a highly potent T cell immunostimulatory factor. It is a soluble form of LAG-3 that binds, with high affinity, to MHC class II molecules expressed by dendritic cells and monocytes. This binding leads to dendritic cells maturation, migration to the lymph nodes and enhanced cross-presentation of antigens to T cells. As a result, strong and sustained anti-tumor or anti-viral cytotoxic T cell responses are obtained.

More than 600 subcutaneous injections of IMP321 have been administered to date in Europe and the USA at doses up to 30 mg with no clinically significant drug-related adverse events. A Phase I trial in metastatic renal cell carcinoma with IMP321 alone has been completed. A Phase I/II trial in metastatic breast cancer combining IMP321 with weekly paclitaxel in a chemo-immunotherapy protocol has been completed. Three Phase I/II clinical trials are in progress: in pancreatic cancer combining IMP321 with gemcitabine in chemoimmunotherapy, a disease-free melanoma study with IMP321 as a therapeutic vaccine adjuvant to peptide antigens, and a lympho-depletive/adoptive transfer metastatic melanoma study.

## INOVIO BIOMEDICAL CORPORATION (INO)

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Phone: 267-440-4200  
Fax: 267-440-4242  
Website: <http://www.inovio.com>

### MANAGEMENT

- J. Joseph Kim, Ph.D., President, Chief Executive Officer, Director
- Peter Kies, Chief Financial Officer
- Mark L. Bagarazzi, Chief Medical Officer
- Kevin W. Rassas, Senior Vice President, Business Development & President, VGX Animal Health
- Niranjan Y. Sardesai, Ph.D., Senior Vice President, Research & Development

### DESCRIPTION

Inovio is a leader in electroporation-delivered DNA vaccines and possesses unique development expertise and proprietary technology and patents in the areas of DNA vaccine design, formulation, and delivery, with related manufacturing expertise as well.

The company's novel SynCon™ DNA vaccine construct technology enables the development of DNA vaccines better able to address changing strains of diseases such as HIV, HCV, HPV, and influenza. Inovio's R&D team has been able to repeatedly translate candidate vaccines, from "bench to IND filing" within one year. Inovio has a broad pipeline of proprietary preclinical and clinical-stage DNA vaccines. Inovio or its partners are conducting Phase I trials in breast, colorectal, ovarian, lung, prostate, melanoma, and cervical (HPV) cancer.

Current partners using the company's electroporation delivery technology include vaccine giant Merck; biotech companies; as well as government and non-government agencies such as the HIV Vaccine Trials Network, National Cancer Institute, and International AIDS Vaccine Initiative.



Charts courtesy of StockCharts.com

## JUVARIS BIOTHERAPEUTICS, INC. (PRIVATE)

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<http://www.juvaris.com>

### MANAGEMENT

- Grant E. Pickering, President and Chief Executive Officer
- Thomas P. Monath, M.D., Chief Medical Officer (Acting)
- Kimberlee Gonzaga, CPA, Chief Financial Officer
- Lee B. Bussey, Ph.D., Sr. Vice President, Manufacturing
- Jeff Fairman, Ph.D., Co-Founder, Vice President, Research

### DESCRIPTION

Juvaris is developing JVRS-100, a cationic lipid-DNA complex, as an immunotherapeutic to treat acute leukemias. JVRS-100 induces profound induction of innate immunity via stimulation of both toll-like receptors and cytosolic interferon induction pathways. JVRS-100 provides greater immune stimulation than known immune stimulants, increasing induction of TH1 cytokines and natural killer (NK) cells. JVRS-100 has demonstrated in vivo efficacy in viral, bacterial and cancer models, in multiple animal species including primates.

JVRS-100 has demonstrated effectiveness in experimental leukemia animal models and is advancing into clinical development with grant funding from a leading academic institution. JVRS-100 is the subject of a Phase I study in leukemia.

Juvaris' immunotherapy technology is also being developed by Bayer HealthCare AG for the treatment of infectious disease and cancer for companion animals in the veterinary field. Programs are underway to develop immunotherapies to treat and/or prevent disease in a variety of animal species.

## MANNKIND CORPORATION (MNKD)

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### MANAGEMENT

- Alfred E. Mann, Chairman of the Board and Chief Executive Officer
- Hakan S. Edstrom, President and Chief Operating Officer
- Matthew J. Pfeffer, Corporate Vice President and Chief Financial Officer
- Juergen A. Martens, Ph.D., Corporate Vice President of Technical Operations and Chief Technical Officer

### DESCRIPTION

MannKind has initiated a Phase 1 clinical study for an investigational cancer immunotherapy. This is a multicenter, open label clinical trial of immune response, safety and tolerability of DNA vector pPRA-PSM with synthetic peptides E-PRA and E-PSM in subjects with advanced solid malignancies.

MKC1106-PP is a DNA vector with two synthetic peptides delivered via a plasmid prime-peptide boost treatment. The clinical study is designed to target two tumor-specific antigens, preferential antigen of melanoma (PRAME) and prostate specific membrane antigen (PSMA), on the basis of their level of expression in commonly occurring adult malignancies, such as ovarian, prostate, renal, pancreatic, breast and colon carcinomas as well as in melanoma.

One of the distinctive features of the company's approach is the delivery method. In contrast to the conventional subcutaneous or intramuscular route of administration, MannKind's compounds are delivered directly into the patient's lymph nodes, sites rich in T-cells and APC. The company believes that this delivery method ensures that T-cells are exposed to greater concentrations of antigens for a longer period of time than would occur after administration by other routes.



Charts courtesy of StockCharts.com

## MOLMED S.P.A. (MLM.MI)

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Website: <http://www.molmed.com>

### MANAGEMENT

- Claudio Bordinon, MD, President and CEO
- Enrico Cappelli, BEC, Chief Financial Officer

### DESCRIPTION

MolMed S.p.A. is a medical biotechnology company focused on discovery, R&D, and clinical validation of innovative therapies for the treatment of cancer. MolMed's M3TK therapy is based on the use of patient's own T lymphocytes, genetically engineered *ex vivo* to express the tumour antigen MAGE-3 and acting as antigen carriers for efficient loading of dendritic cells *in vivo*. This vaccination strategy induces protective immunity and long-term memory, correlated with clinical benefit observed in melanoma patients. Beside melanoma, M3TK has a therapeutic potential in other solid tumours expressing MAGE-3, namely lung, head-and-neck, and oesophageal cancer. MolMed's strategic partner Takara Bio Inc. (Japan) is developing M3TK for the Asian markets.

According to R&D Focus Drug News, in March 2009, Germano Ferrari, Business Development Manager at MolMed, informed R&D Focus that the company's therapeutic cancer vaccine M3TK, is available for worldwide licensing. MolMed halted enrollment into a phase I/II trial of the vaccine in patients with advanced melanoma second half 2008 and suspended the program to focus on priority programs.

## NORTHWEST BIOTHERAPEUTICS, INC. (NWBO.OB)

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Phone: 240-497-4060  
Website: <http://www.nwbio.com>

### MANAGEMENT

- Linda Powers, Chair of the Company's Board of Directors

### DESCRIPTION

Northwest Biotherapeutics, Inc. is developing DCVax<sup>®</sup>, which uses dendritic cells extracted from the body and loaded with tumor biomarkers or "antigens", thereby creating a personalized therapeutic vaccine. Injection of these cells back into the patient initiates a potent immune response against cancer cells, resulting in delayed time to progression and prolonged survival. The Company's lead product candidate is DCVax<sup>®</sup>-Brain which targets Glioblastoma Multiforme (GBM), the most lethal form of brain cancer. DCVax<sup>®</sup>-Brain is manufactured using a patient's own dendritic cells, loaded with a tumor cell lysate prepared from surgically resected tumor tissue. DCVax<sup>®</sup>-Brain has entered a Phase II FDA-allowed clinical trial, which is designed and powered as a pivotal trial. Following this trial, the Company anticipates filing a biologic license application (BLA) with the FDA for DCVax<sup>®</sup>-Brain.

In January 2005, the company received clearance from the FDA to initiate a Phase III trial of DCVax<sup>®</sup>-Prostate, which targets hormone independent (i.e. late stage) prostate cancer. DCVax<sup>®</sup>-Prostate is manufactured using a patient's own dendritic cells, loaded with a recombinant form of Prostate Specific Membrane Antigen (rPSMA). The dendritic cells are generated from monocytes obtained through a single leukapheresis. A Phase I/II study evaluated 32 patients with hormone independent prostate cancer, both non-metastatic and metastatic. In the non-metastatic group of patients (n=12), none had progressed at 28 weeks and only half had progressed at 59 weeks. According to ClinicalTrials.gov, the Phase III trial for DCVax<sup>®</sup>-Prostate was terminated (update June 23, 2005).



Charts courtesy of StockCharts.com

## NOVARX CORPORATION (PRIVATE)

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### MANAGEMENT

- Justin Murdock, Chief Executive Officer
- Habib Fakhrai, Ph.D., Chief Scientific Officer
- Edward Bjurstrom, Senior Vice President of Manufacturing and Operations

### DESCRIPTION

NovaRx Corporation is a clinical-stage biopharmaceutical company dedicated to the discovery, development, and commercialization of novel cell-based therapeutic vaccines for the treatment of cancer. The company was founded in May 1997 in order to commercialize the award-winning research of Dr. Habib Fakhrai and his associates at the Sidney Kimmel Cancer Center in San Diego and at the UCLA School of Medicine in Los Angeles.

NovaRx's lead product candidate is Lucanix<sup>®</sup>, a whole cell-based vaccine comprised of four allogeneic cell lines. Lucanix<sup>®</sup> has successfully completed two Phase II clinical trials for the treatment of advanced stage (IIIB and IV) non-small cell lung cancer (NSCLC). NovaRx has initiated the pivotal Phase III trial under a Special Protocol Assessment (SPA). The trial is being conducted in the US, Canada, and Europe.

Lucanix<sup>®</sup> consists of four NSCLC cell lines gene-modified to block the secretion of TGF- $\beta$ , which is commonly produced by cancer cells. The molecule allows cancer to hide from the body's natural immune system. When TGF-beta is blocked, the immune system can see, find, and destroy the cancer naturally. In a Phase II clinical trial, advanced stage NSCLC patients (stages IIIB and IV) who had received zero to five prior chemotherapies, demonstrated a one-year survival of 61% and a two-year survival of 41%, and a median survival of 16 months.

## ONCOTHYREON, INC. (ONTY)

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Website: <http://www.oncothyreon.com>

### MANAGEMENT

- Robert L. Kirkman, MD, President & CEO
- Gary Christianson, PE, Chief Operating Officer
- Diana Hausman, MD, Vice President, Clinical Development
- Scott Peterson, PhD, Vice President, Research and Development

### DESCRIPTION

Formerly Biomira of Canada, Oncothyreon is a biotechnology company developing Stimuvax<sup>®</sup>, a therapeutic vaccine designed to stimulate an individual's immune system to recognize cancer cells and control the growth and spread of cancers in order to increase the survival of cancer patients. Stimuvax<sup>®</sup> incorporates a 25-amino acid sequence of the cancer-associated marker MUC-1 in a liposomal formulation to stimulate a T-cell mediated immune response.

The company is also developing ONT-10, a preclinical therapeutic vaccine candidate designed to stimulate an individual's immune system to identify cancer cells and mount an immune response against those cells. ONT-10 is a liposomal vaccine composed of a 40 amino acid glycoprotein sequence of the cancer-associated marker MUC-1. The ONT-10 adjuvant is a fully synthetic form of lipid A and is proprietary to Oncothyreon. IND enabling studies of ONT-10 are currently underway at Oncothyreon.

In March 2010, Oncothyreon and its partner Merck Serono temporarily suspended the worldwide clinical development program for Stimuvax<sup>®</sup> based on an unexpected serious adverse reaction in a patient with multiple myeloma participating in an exploratory clinical trial. The suspension affects Phase 3 programs in both non-small cell lung cancer and breast cancer.



Charts courtesy of StockCharts.com

## OXFORD BIOMEDICA PLC (OXB.LSE)

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### MANAGEMENT

- John Dawson, Chief Executive Officer
- Andrew Wood, Chief Financial Officer
- Nick Woolf, Chief Business Officer
- Stuart Naylor, Chief Scientific Officer

### DESCRIPTION

Oxford BioMedica and its collaborators are developing novel targeted therapies and therapeutic vaccines to treat multiple types of cancer. TroVax<sup>®</sup> is the company's therapeutic vaccine that stimulates the immune system to destroy cancerous cells expressing the 5T4 tumor antigen, a unique protein found on most common types of solid cancer, which makes it a potentially valuable target for novel anti-cancer interventions. The product is based on an attenuated modified vaccinia virus Ankara (MVA), engineered to deliver the 5T4 antigen.

A Phase III trial in advanced and metastatic renal cell carcinoma started in November 2006 and reached full recruitment of 733 patients in March 2008. The study was amended in July 2008, following the recommendation of the Data Safety Monitoring Board (DSMB) that it would not meet the predefined primary efficacy endpoint of survival improvement. The DSMB recommended that patients continue to be monitored without further vaccinations. The Company gained valuable insights for optimizing the design of further trials from the Phase III TRIST study in renal cancer, and is preparing to start new studies in 2010. The Company is also targeting new Phase II trials of TroVax<sup>®</sup> in prostate cancer.

## PRIMA BIOMED LTD. (PRR.AX)

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AUSTRALIA,3143  
Phone: +61 3 9824 5254  
Fax: +61 3 9822 7735  
Website: <http://www.primabiomed.com.au>

### MANAGEMENT

- Matthew Lehman, Chief Operating Officer
- Dr Neil Frazer, Chief Medical Officer
- Ginny Raymond, Clinical Affairs Director

### DESCRIPTION

Prima BioMed is focused on technologies in the fields of cancer immunotherapy and immunology. Prima's lead product is the CVac™, a MUC1 dendritic cell vaccine for ovarian cancer therapy treatment. It has completed two successful clinical trials and is progressing toward eventual commercialization in the United States, Australia, Europe, and globally.

The CVac™ product consists of an adjuvant, the so-called "mannan", a string of modified mannose (a sugar) units created with mucin-1 and dendritic cells cultured from the patient's immune system. The cells are allowed to multiply in the laboratory and are then prepared for the physician or nurse to inject into the surface of the skin in 6 to 8 places.

Prima BioMed is planning a randomized, open-label Phase IIb trial of maintenance therapy with CVac for epithelial ovarian cancer patients in first or second remission. Patients will receive vaccinations every four weeks for 24 weeks followed by booster injections every eight weeks until week 48.

Prima BioMed has also developed an adjuvant based on nanoparticles made of polystyrene or a biodegradable material for use in vaccines ("DCTag™" technology).

## PROGENICS PHARMACEUTICALS, INC. (PGNX)

777 Old Saw Mill River Road  
Tarrytown, NY 10591  
Phone: 914-789-2800  
Fax: 914-789-2817  
Website: <http://www.progenics.com>

### MANAGEMENT

- Paul J. Maddon M.D., Ph.D., Founder, Chief Executive Officer and Chief Science Officer
- Mark R. Baker J.D., President
- Robert A. McKinney, CPA, Senior Vice President, Finance and Operations & CFO
- Thomas A. Boyd, Ph.D., Senior Vice President, Product Development
- Robert J. Israel M.D., Senior Vice President, Medical Affairs
- William C. Olson, Ph.D., Senior Vice President, Research and Development

### DESCRIPTION

In November 2008, Progenics announced plans to initiate a 29-week, phase 1, multi-dose, dose-escalation study of a therapeutic vaccine for prostate cancer, PSMA-VRP. PSMA-VRP is designed to induce both antibodies and killer T-cells that can recognize and potentially eliminate prostate-specific membrane antigen (PSMA)-positive prostate cancer cells in a vaccinated patient. The PSMA-VRP vaccine is based on the platform alphavirus replicon vector technology system developed under license from AlphaVax, Inc.

Progenics has also developed a subunit vaccine based on a novel rsPSMA protein that represents the entire extracellular domain of PSMA. The vaccine comprises purified rsPSMA protein formulated with Alhydrogel® adjuvant. Based on abstract #2572 from the 2005 ASCO annual meeting proceedings, the rsPSMA protein vaccine has been advanced into a dose-escalating Phase I clinical trial in advanced prostate cancer.

According to Progenics' Form 10-K filed March 15, 2010, both the PSMA-VRP and rsPSMA immunotherapy product candidates are still in Phase I trials.



Charts courtesy of StockCharts.com

## PROVECTUS PHARMACEUTICALS, INC. (PVCT.OB)

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Phone: 866-594-5999  
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### MANAGEMENT

- Craig Dees, Ph.D., Chief Executive Officer
- Timothy Scott, Ph.D., President
- Eric Wachter, Ph.D., Executive Vice President
- Peter R. Culpepper, CPA, MBA, Chief Financial Officer, Chief Operating Officer

### DESCRIPTION

Provectus is developing PV-10, a proprietary, injectable formulation of Rose Bengal, a compound that has been in use for nearly thirty years by ophthalmologists to assess damage to the eye. It has also been used as an intravenous diagnostic to detect ailments of the liver. Rose Bengal is a small molecule agent with an established safety history, a short half-life in the bloodstream, and is excreted via the liver and kidneys. Provectus has discovered a novel use for Rose Bengal based on the observation that it is selectively toxic to cancer cells via a process called chemoablation whereby cells undergo a form of cell death that mimics both features of necrosis and apoptosis. Localized increases in mononuclear tumor-infiltrating lymphocytes suggest that tumor necrosis releases antigens to nearby antigen-presenting cells, facilitating presentation of antigenic targets to T-cells and B-cells.

Provectus is currently conducting a Phase II trial to investigate the effectiveness of intralesional PV-10 for locoregional treatment of metastatic melanoma. This study will also include assessment of response in untreated bystander lesions following intralesional injection of PV-10 into targeted lesions. Data from the Phase II study of has been accepted for presentation at the 2010 American Society of Clinical Oncology (ASCO) Scientific Program to be held on June 4 – 8, 2010 in Chicago, Illinois.



Charts courtesy of StockCharts.com

## QUANTUM IMMUNOLOGICS, INC. (PRIVATE)

1881 W. Kennedy Blvd.  
PO Box 20727  
Tampa, FL 33623-0727  
Phone: 813-849-7885  
Website: <http://www.quantumimmunologics.com>

### MANAGEMENT

- Josh Coughlin, President
- Barry Rooth, JD, Executive VP; President of QI Ventures, Inc.
- Taina Broes, Senior VP; Director of Operations
- Don Wright, MBA, CMA, Senior VP; Director of Finance
- Tim Schwiers, VP; Director of Auburn Collaboration

### DESCRIPTION

Quantum Immunologics, Inc. is developing the universal tumor antigen oncofetal antigen/immature laminin receptor protein (OFA/iLRP) in a dendritic cell based vaccine. OFA/iLRP is a logical target for immunotherapy because it has been found to be expressed in all human, as well as, murine cancers examined so far, which includes myeloid and lymphoid leukemias, lymphomas, renal cell carcinomas, prostate cancer, breast cancer, lung cancer, melanoma, squamous cell carcinoma, and ovarian cancer. It is not found on normal tissue after mid-gestation in fetal development. The 37 kDa OFA/iLRP is a highly conserved protein in humans, rodents, and other species.

A Phase I/II trial in metastatic breast cancer is underway to examine the inherent immune response in breast cancer patients directed towards OFA/iLRP and whether this immune response could be amplified and modified through actively vaccinating using autologous OFA/iLRP-pulsed dendritic cells reinjected into cancer patients.

## TRANSGENE SA (TNG.PA)

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Fax: +33 (0)3 88 27 91 11  
Website: <http://www.transgene.fr>

### MANAGEMENT

- Philippe Archinard, Chief Executive Officer
- Philippe Poncet, Chief Financial Officer
- Jean-Yves Bonnefoy, Vice-President, Research and Development
- Thibaut Du Fayet, Vice President, Business Development & Marketing

### DESCRIPTION

Transgene is developing TG4010 (MVA-MUC1-IL2), which uses the Modified Vaccinia Ankara (MVA) virus vector, a poxvirus that combines distinguishing advantages for an optimized systemic vaccination. MVA is a highly attenuated strain which has been tested extensively in humans as a smallpox vaccine and is known to strongly stimulate innate and adaptive immune responses to antigens. TG4010 expresses the entire MUC1 gene sequence and has the potential to generate an immune response to all antigenic epitopes of MUC1. The sequence coding for the cytokine Interleukin 2 (IL2) is included to help stimulate specific T-cell response.

In March 2010, Transgene signed an exclusive option agreement with Novartis for the development and commercialization of TG4010. Transgene will initially fund and retain control over the next clinical development phase of TG4010, which is a pivotal, global phase IIb/III clinical trial that Transgene currently anticipates starting by the end of 2010. This study will involve approximately 1,000 patients with MUC1-positive NSCLC who have normal levels of activated Natural Killer (NK) cells at time of trial entry. Results from the phase IIb portion of this combined phase IIb/III clinical trial are expected to be available in the first quarter of 2012. The final results are expected to become available by the end of 2013.

## VACCINOGEN, INC. (PRIVATE)

5300 Westview Drive  
Suite 406  
Frederick, MD 21703  
Website: <http://www.vaccinogeninc.com>

### MANAGEMENT

- Michael G. Hanna, Jr., Ph.D., Founder, Chairman & CEO
- Andrew L. Tussing, Co-Founder, COO & Corporate Secretary
- H.C. Hoover, Jr., M.D., Senior Medical Advisor

### DESCRIPTION

Vaccinogen is a biotechnology company with more than three decades of research into combating cancer by using the body's own immune system. It is the producer of OncoVAX<sup>®</sup>, the only immunotherapy for Stage II colon cancer. OncoVAX<sup>®</sup> is an active specific immunotherapy (ASI) that uses the patient's own cancer cells to block the return of colon cancer following surgery. This patient-specific vaccine comprises sterile, metabolically active, irradiated, non-tumorigenic autologous tumor cells, with or without fresh frozen Bacillus Calmette-Guerin ("BCG") bacterial as an adjuvant. Vaccinogen's scientists prepare a vaccine from the patient's own tumor and then administer the vaccine to the patient by three weekly injections one month after surgery. A fourth "booster" is administered six months later. OncoVAX<sup>®</sup> reduces recurrence and deaths by over 50%.

OncoVAX<sup>®</sup> has successfully completed its first Phase IIIa trial in Stage II colon cancer demonstrating a 25% improvement in 5-year median overall survival; 39% improvement in 5-year median recurrence-free survival; and 64% decrease in the number of patients whose disease progressed 18 months following treatment.

OncoVAX<sup>®</sup> currently has a marketing authorization from Swissmedic, Switzerland's medical authority, in the category of "procedes therapeutiques." This authorization permits foreign and domestic Swiss patients to purchase OncoVAX<sup>®</sup> on a self-pay basis.

## VAXONCO, INC. (PRIVATE)

2<sup>nd</sup> Fl Ria B/D  
912-18 Daechi-Dong  
Gangnam-gu, Seoul, Korea  
Website: <http://www.vaxonco.com>

### MANAGEMENT

- Dr. Jay Sangjae Kim, Chairman of the Board and CEO

### DESCRIPTION

VaxOnco Inc, a Korean specialty biotechnology company focused on peptide based cancer vaccines, acquired of all intellectual property rights for Onyvax-P (ONY-P), a cell vaccine in development for prostate cancer by Onyvax. ONY-P is a new investigational vaccine treatment designed to stimulate the immune system to attack prostate cancer. ONY-P consists of a combination of cell lines that are representative of different stages of the disease. The cells have been inactivated and cannot grow or reproduce to create a new cancer.

ONY-P for prostate cancer has been the subject of three randomized, controlled Phase IIb studies in patients who have no radiologically detectable disease. In an earlier Phase IIa proof-of-principle study, primary endpoints were met (Clin Cancer Res (2005) 11:4469-4478): the median progression free survival was 58 weeks, which compares favorably with historic control data of 26-29 weeks. 42% patients experienced a prolonged, statistically significant reduction in prostate specific antigen velocity (independent studies have shown PSA velocity to be a predictor of overall survival). The treatment was very well tolerated and side effects were minimal. An earlier Phase I/II study in advanced metastatic disease demonstrated safety, tolerability and immunogenicity, with patients showing increased T-cell and antibody responses against tumor targets. In 2009 VaxOnco acquired the US subsidiary of Pharmexa A/S – Pharmexa-Epimmune - and it already has separate technology licensing agreements in leukemia research with key US institutions such as the Rush University Medical Center in Chicago.

## VICAL INCORPORATED (VICL)

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### MANAGEMENT

- Vijay B. Samant, President and Chief Executive Officer
- Jill M. Broadfoot, Senior Vice President, Chief Financial Officer and Secretary
- Alain P. Rolland, Pharm. D., Ph.D., Executive Vice President, Product Development
- Kevin R. Bracken, Vice President, Manufacturing
- Richard T. Kenney, M.D. Vice President, Clinical Development
- Larry R. Smith, Ph.D., Vice President, Vaccine Research

### DESCRIPTION

Vical is developing Allovectin-7<sup>®</sup>, a plasmid/lipid complex containing the DNA sequences encoding HLA-B7 and  $\beta 2$  microglobulin, which together form a major histocompatibility complex, or MHC, class I. The company believes injection of Allovectin-7<sup>®</sup> directly into tumor lesions directs an immune response against metastatic tumors through several mechanisms. In HLA-B7 negative patients, a vigorous allogeneic immune response may be initiated against the foreign MHC class I antigen. In all patients,  $\beta 2$  microglobulin may reconstitute normal class I antigen presentation and/or increase tumor antigen presentation to the immune system. In any patient, an innate pro-inflammatory response may occur that induces tumor responses following intralesional injection of the DNA/lipid complex. The goal of all three of these mechanisms is to initially cause recognition of the tumor at the local site to allow a then sensitized immune response to recognize un-injected tumors at distant metastatic sites.

In January 2007, Vical initiated a Phase III pivotal trial under a Special Protocol Assessment, or SPA, with the FDA for certain patients with stage III or stage IV melanoma. AnGes MG, Inc. is funding the Phase III trial under a collaborative R&D agreement signed in May 2006.



Charts courtesy of StockCharts.com

## APPENDIX D: IDEC PHARMACEUTICALS - ANATOMY OF A SUCCESS

A pioneer in the field of passive cancer immunotherapy, Idec Pharmaceuticals, Inc. made its stock market debut in September 1991 with an initial public offering of 3 million shares of common stock at \$15 per share. The company raised \$52 million to support research and development activities and ended its first day of trading with a market capitalization in excess of \$150 million.

Despite its initial success, Idec's stock would succumb to the biotech bear market of 1992. In the years that followed, the company's stock hit an all-time low of \$2 1/8 and its market capitalization fell below \$30 million.

In November 1997, the company received FDA approval for the first mAb for cancer therapy, Rituxan®. Developed by Idec Pharmaceuticals, Rituxan® is a chimeric monoclonal antibody against the protein CD20 that is currently approved for the treatment of CLL, NHL, and RA.

In 1999, Idec's stock traded at a new all-time high at \$140 and garnished a market capitalization above \$3.3 billion. Not bad for a company that just reported its first year of profitability and \$87 million in revenue for 1998.

Today, many biotech companies developing active cancer immunotherapies face the same hurdles that Idec did in 1994 - low share price, micro-market capitalizations, negative earnings per share and little (if any) coverage from Wall Street analysts. Accordingly, this section is devoted to a chronicle of Idec Pharmaceuticals from its inception as a publicly traded company in 1991 through commercial introduction of the first passive immunotherapy product for the treatment of cancer. Significant corporate developments and the closing stock price at the time are listed for each year. By examining how Idec overcame adversity to become a Wall Street success story, individuals should be better equipped to survey the current small capitalization segment of the biotech sector in search of similar "fallen angels".

## 1991

9/17/91 - Idec Pharmaceuticals makes its stock market debut in an IPO priced at \$15. The stock climbs to a high of \$19 per share its first day of trading. (\$18.75)

12/5/91 - Company announces goal to enter human clinical studies in 1992 for pan B antibodies conjugated with the radioisotope yttrium for the treatment of advanced non-Hodgkin's B-cell lymphomas. (\$12.25)

## 1992

1/16/92 - Receives clearance to begin Phase I human clinical study using the first monoclonal antibody-based therapy for HIV (known as 3C9). (\$19.00)

2/12/92 - Announces plans to unify all company operations in one location by expanding to a new headquarters site in the San Diego area. (\$13.25)

2/24/92 - Five products undergoing human testing: Specifid™, a panel of anti-idiotypic antibodies in Phase III studies for non-Hodgkin's B-cell lymphomas; yttrium conjugated anti-ids, in Phase I/II studies for advanced-stage lymphomas; I-Mel-1 and I-Mel-2, therapeutic vaccines in Phase I/II studies for malignant melanoma; and 3C9, a therapeutic vaccine for use in treating HIV infection. (\$13.75)

3/26/92 - Announced the development of "primatized" antibodies derived from human and macaque monkey antibodies. (\$11.50)

4/10/92 - Many biotech IPO's from 1991 are now trading below their offering price. (\$9.00)

5/20/92 - According to SEC filing, The State of Wisconsin Investment Board raised its stake in Idec to 6.1% of common shares outstanding (522,700 shares) including 354,000 shares purchased at prices ranging from \$6.63 to \$13.38 per share. (\$7.00)

5/27/92 - According to SEC filing, The State of Wisconsin Investment Board now owns 622,700 shares of Idec after purchasing 100,000 shares on May 13 at \$6.88. (\$7.25)

6/9/92 - According to SEC filing, The State of Wisconsin Investment Board now owns 710,400 shares of Idec including 87,700 shares purchased on May 20 and May 21 at \$6.25 and \$6.88 per share. (\$8.00)

6/11/92 - Receives FDA authorization to begin human testing of Specifid™ antibodies manufactured by Boehringer Ingelheim Int'l. Pivotal Phase III human study expected to begin in 1992. (\$8.125)

7/1/92 - Announces positive interim Phase I/II results from I-Mel-1 and IMel-2 melanoma vaccines. Larger trials are necessary to demonstrate efficacy. (\$7.00)

10/14/92 - Idec and SmithKline Beecham enter into a product development and marketing agreement for the commercialization of therapeutic products based on “primatized” anti-CD4 antibodies. Potential applications include rheumatoid arthritis, psoriasis, systemic lupus erythematosus and others. Idec could receive in excess of \$30 million in milestone payments plus funding for research and development. Additionally, Idec will receive royalties on product sales resulting from the collaboration. SmithKline’s venture capital subsidiary agreed to purchase \$2.4 million worth of Idec’s stock through open market purchases plus warrants to purchase up to 400,000 shares of stock at \$12 per share. (\$8.25)

## 1993

2/22/93 - Idec and SmithKline expand collaboration to include Asia. Idec will receive up to \$20 million in additional payments. Additionally, Idec initiates Phase I/II human clinical testing for a genetically engineered “pan-B” antibody for lymphoma immunotherapy and will soon begin human testing of a yttrium-conjugated pan-B antibody for targeted radiation therapy. Idec also filed a Phase III pivotal study protocol for Specifid™ antibodies with the FDA. (\$7.00)

6/17/93 - Receives patent for Melimmune(TM)-2 therapeutic vaccine for melanoma. Idec plans a Phase II study in inoperable disease in late 1993 and a pivotal Phase III study in post-surgery melanoma patients in 1994. (\$5.50)

7/22/93 - Idec discontinues development of Specifid™ product candidate. The company states that the Specifid panel of 15 antibodies targets cell-surface markers present only in 25% of patients with non-Hodgkin's B-cell lymphoma. In contrast, the company's pan-B agents target markers present in over 90% of lymphomas. Based on encouraging clinical data, Idec begins preparation for a Phase I/II study of the pan-B antibody for the treatment of relapsed B-cell lymphoma. Additionally, the company initiated human clinical testing of a radiolabeled, therapeutic pan-B antibody. (\$4.25)

8/3/93 - Company receives FDA clearance to begin human testing of Primatized™ anti-CD4 antibody for treatment of rheumatoid arthritis. This event triggers a six-month period during which SmithKline's venture subsidiary will make open-market purchases totaling \$1.2 million of Idec's common stock and 200,000 warrants that may be converted into common stock for \$12 per share. (\$4.75)

10/4/93 - Company reports that Melimmune(TM)-2 stimulates both antitumor killer cells and antibodies. In addition, Idec plans to combine Melimmune-1 and Melimmune-2 into a single product candidate called Melimmune. This new combination therapy will be tested in a Phase I/II study this month, with a pivotal Phase III protocol expected to begin as early as 3Q 1994. (\$5.25)

12/7/93 - A Phase I safety trial of Idec's pan-B antibody (Idec-C2B8) involving 15 patients showed tumor shrinkage in two-thirds of the patients. (\$7.25)

1994

2/11/94 - Punk Ziegel & Knoell initiates coverage of Idec with a "buy" rating. According to Dow Jones News Service, Punk Ziegel's research note stated that Idec-C2B8 is potentially a \$200 million drug and that Idec could be profitable for 1998. (\$5.563)

3/4/94 - Idec and Mitsubishi Kasei announce collaboration on Primatized™ antibody directed at a marker known as B7. Anti-B7 antibodies may be effective in immune system diseases. (\$4.875)

3/4/94 - Idec files registration statement for 2,750,000 newly issued common shares directly to institutional investors. (\$4.875)

4/25/94 - Initiates Phase II trial of Idec-C2B8 in combination with chemotherapy for the treatment of relapsed, low-grade, B-cell lymphoma. (\$3.375)

4/28/94 - Idec decides to postpone marketing the direct placement of 2,750,000 shares of common stock due to current stock market conditions and trading price of Idec's stock. Idec exercises an option to receive \$5 million in equity funding during 1994 from SmithKline Beecham. (\$3.375)

5/25/94 - Based on clinical activity in a Phase I safety trial, Idec initiates Phase I/II trial for Idec-CE9.1 for rheumatoid arthritis. (\$3.875)

6/16/94 - Idec decides to proceed with the direct placement of 2,800,000 shares of common stock at \$2.75 per share to a group of institutional investors. 600,000 shares of the offering are being purchased by SmithKline. (\$3.125)

10/27/94 - Idec reports positive Phase II results for Idec-C2B8 in treatment of lymphoma. 22 of 34 patients with relapsed disease experienced tumor shrinkage. (\$2.625)

## 1995

1/3/95 - Idec receives \$13.35 million in financing, which includes \$3.35 million in equity purchases by SmithKline at approximately \$2.39 per share and a \$10 million lease financing agreement. (\$2.375)

2/2/95 - Idec and Seikagaku announce collaboration worth up to \$26 million plus royalties to develop Primatized™ anti-CD23 antibodies for the treatment of allergic rhinitis and asthma. (\$2.813)

3/16/95 - Idec announces collaboration with Genentech to develop and commercialize Idec-C2B8 for the treatment of non-Hodgkin's B-cell lymphomas. The potential value of the agreement is \$57 million in milestone payments and equity investments. Idec will also receive a

share of profits in the U.S. and Canada, while receiving royalties on sales outside these territories. Idec expects the product to enter pivotal Phase III trials in 1995, with completion set for 1996 and FDA submission by 1997. (\$4.50)

3/17/95 - Punk Ziegel & Knoell upgrades Idec to “aggressive buy” from “buy”. (\$4.125)

4/27/95 - Idec initiates pivotal Phase III trial of Idec-C2B8. (\$4.00)

10/20/95 - According to Dow Jones News Service, Morgan Stanley initiates research coverage of Idec with an “outperform” rating. (\$10.75)

10/23/95 - Idec announced positive results from a multi-dose Phase I/II trial of Idec-CE9.1 for rheumatoid arthritis. A larger Phase II trial has already been implemented. (\$10.625)

11/1/95 - Idec reports positive preliminary results combining Idec-C2B8 with chemotherapy. (\$14.50)

11/20/95 - Forbes article highlights Idec’s new treatment for lymphoma. (\$12.75)

12/4/95 - Idec and Genentech expand lymphoma collaboration to include Japan and Asia. (\$14.375)

## 1996

1/3/96 - Idec and Eisai Co. of Japan form collaboration worth up to \$37.5 million plus royalties for Primatized™ anti-gp39 antibodies for the treatment of autoimmune diseases. (\$20.375)

1/10/96 Idec gets contract manufacturing pacts from Merck & Co., OraVax Inc. and Pharmacia & Upjohn. (\$17.75)

2/20/96 - Idec and Genentech expand lymphoma collaboration to include Idec-Y2B8, which is an anti-CD20 antibody coupled to the high-energy radioisotope, yttrium90. Phase II clinical testing is expected to begin in 1996. (\$19.25)

3/7/96 - Idec completes patient accrual for Idec-C2B8 Phase III pivotal trial, with results expected in late 1996. (\$18.125)

3/13/96 - Idec updates positive lymphoma trial results for Idec-C2B8. According to Dow Jones News Service, Morgan Stanley raises its rating on Idec to “strong buy” from “outperform”. (\$21.125)

4/2/96 - Chugai Pharmaceutical of Japan licenses Idec’s technology for high-yield gene expression. (\$25.00)

5/3/96 - Idec files for a public offering of 1.5 million shares of common stock being managed by Morgan Stanley and Punk, Ziegel & Knoell. (\$27.125)

5/13/96 - Genentech accelerates its purchase of an additional \$7.5 million in shares of Idec’s convertible preferred stock. The purchase was originally scheduled to coincide with the public presentation of complete Phase III results of Idec-C2B8 for lymphoma due in December of 1996. Interim results from the first 50 patients of this pivotal trial will be presented on May 21, 1996. (\$30.125)

5/21/96 - Idec announces positive preliminary results for Idec-C2B8 at the annual meeting of the American Society of Clinical Oncology. (\$29.625)

6/7/96 - Idec announces the effectiveness of its public offering of 1.8 million shares priced at \$24 per share. (\$23.875)

6/25/96 - According to Dow Jones News Service, Morgan Stanley reinstates coverage of Idec with a “strong buy” rating and 12-month price target of \$40. (\$23.50)

7/25/96 - Announces second quarter results and announces that SmithKline unblinded a 143-patient Phase II study of Idec-CE9.1 for rheumatoid arthritis and observed positive clinical activity. Final results of the Phase II trial will be presented in October. (\$15.875)

8/12/96 - Idec initiates Phase I/II trial incorporating its lead product Idec-C2B8 and its yttrium labeled radioimmunotherapy product - Idec-Y2B8. (\$19.125)

10/21/96 - Idec announces that the Phase II trial of Idec-CE9.1 for the treatment of rheumatoid arthritis showed the product was safe and efficacious. (\$22.375)

10/30/96 - Idec reports third quarter results and announces that pivotal Phase III trial results of Idec-C2B8 will be presented at the American Society of Hematology conference, which runs from December 6-10, 1996. Additionally, Idec reports that based on positive Phase II results, SmithKline plans to initiate Phase III trials of Idec-CE9.1 for rheumatoid arthritis within the next several weeks. (\$20.75)

12/3/96 - Idec and SmithKline initiate Phase III trial of Idec-CE9.1 for treatment of rheumatoid arthritis. (\$25.00)

12/9/96 - Idec and Genentech report positive final results for pivotal Phase III trial of Idec-C2B8. A BLA filing for Idec-C2B8 as a single agent therapy for relapsed patients with low grade or follicular non-Hodgkin's lymphoma is expected in the first half of 1997. (\$23.625)

12/13/96 - According to a SEC filing, a group including SmithKline Beecham cut its stake in Idec to 11.3%. 400,000 common shares were sold between December 2-4 at prices ranging from \$24.19 to \$25.44 per share. The group now holds about 2 million shares of Idec. (\$21.00)

## 1997

1/16/97 - Idec grants Boehringer Ingelheim GmbH of Germany license to technology for high yield protein expression. (\$22.125)

2/12/97 - Idec acquires worldwide rights for broad spectrum anticancer agent (9-aminocamptothecin), currently in Phase II clinical trials, from Pharmacia & Upjohn. (\$21.50)

2/21/97 - According to Dow Jones News Service, CS First Boston initiates coverage of Idec with a "strong buy" rating. (\$23.00)

3/3/97 - Idec, Genentech and Roche submit applications for U.S. & European approval of Idec-C2B8 (rituximab) - the first monoclonal antibody for cancer treatment in the U.S. (\$24.313)

3/3/97 - According to a SEC filing, a group including SmithKline Beecham cut its stake in Idec to 6.1%. 935,000 common shares were sold between February 5-28 at prices ranging from \$22.25 to \$24.88 per share. The group now holds about 1.1 million shares of Idec. (\$24.313)

3/7/97 - According to Dow Jones News Service, Montgomery Securities initiates coverage of Idec with a “buy” rating and one-year price target of 52. (\$26.00)

3/10/97 - According to a SEC filing, investor Larry Feinberg reported a 5.47% stake in Idec. Feinberg said he holds 988,600 common shares, 462,000 of which were purchased between January 28-March 5 at prices ranging from \$20.88 to \$24.83 per share. (\$28.875)

3/18/97 - According to a SEC filing, a group including SmithKline Beecham cut its stake in Idec to 3.5%. 467,500 common shares were sold between March 4-14 at prices ranging from \$24.50 to \$30 per share. The group now holds 638,360 shares of Idec. (\$27.125)

3/20/97 - Protein Design Labs grants license under antibody humanization patents to Idec. (\$25.50)

5/19/97 - Idec and SmithKline announce positive results of a pilot Phase I/II trial of a Primatized® anti-CD4 monoclonal antibody in severe asthma. (\$22.00)

6/18/97 - Merrill Lynch initiates research coverage of Idec at “accumulate”. (\$26.25)

6/19/97 - Idec announces that Idec-C2B8 (rituximab) is scheduled for an advisory committee review meeting on July 25th. (\$26.438)

6/24/97 - Idec and SmithKline suspend further enrollment and treatment in the Phase III and supportive clinical trials of Idec-CE9.1 for rheumatoid arthritis based on lowered CD4 cell counts. (\$23.25)

7/25/97 - According to a SEC filing, investor Larry Feinberg reported a 8.2% stake in Idec. Feinberg said 260,000 shares were purchased between May 29-July 17 at prices ranging from \$22.88 to \$27.85 per share. (\$26.375)

7/25/97 - FDA advisory committee unanimously recommends clearance for marketing of Idec-C2B8 – now known as Rituxan™. (\$26.375)

7/31/97 - Idec adopts shareholder purchase rights plan to guard against abusive takeover tactics. (\$27.25)

8/19/97 - According to Dow Jones News Service, Piper Jaffray initiates coverage of Idec with a “buy” rating and one-year price target of 33. (\$26.00)

8/29/97 - Idec receives 6-month review letter from FDA requesting additional data on certain aspects of the production process related to the bulk drug manufacture of Rituxan™. (\$30.375)

9/4/97 - Idec enters into an arrangement to purchase and sell call options on the company’s common stock. (\$30.75)

10/1/97 - According to Dow Jones News Service, Merrill Lynch upgrades Idec to a “buy” rating from “accumulate” and names Idec the Focus One stock of the week. (\$41.625)

10/3/97 - Idec regains rights to Idec-Y2B8 from Genentech. Genentech states that the company is focusing on other development projects and sees a smaller market opportunity for radioimmunotherapies as compared to Rituxan™. Idec is in early-stage discussions with a potential European development partner for the product. (\$42.875)

11/18/97 - Idec begins Phase I/II clinical trial for 9-aminocamptothecin (9-AC) for various cancers. (\$37.00)

11/26/97 – Rituxan™ receives FDA approval, becoming the first U.S. monoclonal antibody for therapeutic use in cancer. (\$35.00)

12/3/97 - Idec and SmithKline announce positive Phase I trial results of their second generation Primatized™ anti-CD4 antibody - Idec-151. Phase II trials have commenced. (\$36.50)

12/8/97 - Idec grants Kirin Brewery of Japan license to technology for high yield protein expression. (\$37.375)

12/9/97 - Idec reports positive Phase I/II trial results incorporating both Rituxan™ and Idec-Y2B8. Idec anticipates beginning enrollment in a pivotal Phase III trial by early 1998. (\$37.25)

12/16/97 - Idec and Genentech announce that Rituxan™ is being shipped today to the oncology medical community. (\$33.875)

## 1998

2/10/98 - Idec initiates Phase I studies with humanized monoclonal antibody, Idec-131, in patients with systemic lupus erythematosus. (\$43.875)

2/24/98 - Idec files registration statement for public offering of 2 million shares of common stock. (\$41.813)

2/25/98 - Idec initiates pivotal Phase III trial incorporating both Rituxan™ and Idec-Y2B8 for the treatment of relapsed or refractory non-Hodgkin's lymphoma. (\$43.50)

3/2/98 - Idec and SmithKline select Idec-151 (Clenoliximab) as their lead anti-CD4 antibody for the treatment of rheumatoid arthritis. Patient accrual in the Phase II trial is expected to be completed by mid-1998. (\$43.00)

3/4/98 - Idec elects to withdraw its follow-on offering of 2 million shares based on market conditions. (\$39.25)

4/14/98 - Genentech reports first quarter Rituxan™ sales of \$37.7 million. (\$38.875)

6/3/98 – Rituxan™ receives marketing clearance in all European Union countries. (\$30.625)

7/14/98 - Idec announces U.S. Rituxan™ sales of \$32 million in the second quarter. (\$26.625)

10/20/98 - Idec announces U.S. Rituxan™ sales of \$36.1 million in the third quarter. (\$26.25)

10/27/98 - Idec initiates Phase I study of Primatized® antibody, Idec-114, in patients with Psoriasis. (\$27.125)

12/1/98 – Rituxan™ is blamed for eight deaths. (\$30.875)

12/4/98 - SmithKline Beecham agrees to a potential \$132 million collaboration to develop Coulter Pharmaceutical's experimental drug for non-Hodgkin's lymphoma. (\$33.125)

12/11/98 - Idec reports that Rituxan™ sales reached \$103 million during the nine months ended September 30. (\$43.563)

12/23/98 - Idec and SmithKline announce a decision to delay initiation of Phase IIB studies of Idec-151 for rheumatoid arthritis pending an analysis of safety and efficacy data. (\$44.125)

## 1999

1/21/99 - Idec announces U.S. Rituxan™ sales of \$48.8 million in fourth quarter. (\$47.313)

2/2/99 - Idec announces intention of raising \$100 million in zero coupon convertible notes. (\$49.875)

2/2/99 - Idec reports its first year of profitability, earning \$0.92 per share on a diluted basis. Idec also announces that SmithKline has elected to discontinue development of Idec-151 in rheumatoid arthritis and instead will conduct a pilot clinical study with Idec-151 in psoriasis. (\$49.875)

2/16/99 - Idec signs three research collaborations aimed at developing new treatments for solid tumors. (\$41.75)

3/10/99 - Idec is added to the Standard & Poor's SmallCap 600 Index. (\$54.875)

3/31/99 - Idec begins Phase II study of Idec-131 in patients with active systemic lupus erythematosus based on positive Phase I testing. (\$51.375)

4/12/99 - Idec announces U.S. Rituxan™ sales of \$52 million in first quarter. (\$57.50)

6/10/99 - Idec and Schering AG enter licensing agreement valued at \$47.5 million for commercialization of Idec-Y2B8 (now known as Zevalin™). (\$56.25)

7/22/99 - Idec announces U.S. Rituxan™ sales of \$68.3 million in second quarter. (\$83.50)

## APPENDIX E: ABOUT MD BECKER PARTNERS LLC

### WHO WE ARE

MD Becker Partners is a boutique management and strategy consulting firm focusing on both public and private companies in the life sciences industry, including pharmaceuticals, biotechnology, and medical devices. We also work with venture capitalists, institutional investors, and others that provide capital to these companies.

### OUR EXPERIENCE

We believe an organization's most important asset is its people: their skills, relationships, experience and knowledge. The senior partners working on all client accounts have more than 45-years of real-world, in-house experience in the life sciences industry and financial sector. This unique experience in both the scientific and business aspects of biotechnology combined with extensive industry knowledge and close personal relationships provides our firm - and its clients - with a clear competitive advantage.

### WHY WE'RE UNIQUE

As both consultants ourselves and past corporate users of consultants, we believe that many firms are too narrowly focused and too limited to address today's business challenges. While the ability to communicate and access information has improved enormously, too much vital data, knowledge and creative ideas stand alone in traditional silos, preventing companies from reaching their full potential.

As a strategic advisor and partner, everything we do is focused on helping our clients increase visibility, unlock stakeholder value and access resources to grow their business. To accomplish this, we integrate strategy, relations, and operational capabilities and apply them to carefully conceived and expertly enacted tactics. In addition, we limit our client base in order to provide the personalized and dedicated service that only a boutique firm can offer.

## THE TOP 10 PROBLEMS WE SOLVE

Clients often hire us to solve the following corporate challenges:

- Achieving a fair market valuation
- Accessing adequate capital and other resources to achieve corporate goals
- Improving liquidity to overcome low average trading volume
- Applying technology and tools, such as new, digital, and social media
- Entering new markets or geographies
- Attracting partners in today's fiercely competitive marketplace
- Conducting proper due diligence, market research, valuations and competitive analysis
- Outsourcing to address time sensitive projects or convert high fixed expenses into variable costs
- Launching a new (or rejuvenated) product or corporate brand
- Eliminating disconnects between planned and perceived business models or corporate strategies

As a strategic advisor and partner, clients also depend on our objective, third-party perspectives and additional expertise.

## APPENDIX F: MD BECKER PARTNERS MANAGEMENT BIOGRAPHIES

### MICHAEL D. BECKER

Founder, President and Chief Executive Officer

Mr. Becker has more than 15-years of experience as a serial entrepreneur, C-level industry executive, drug developer, Wall Street securities analyst and registered financial advisor. He is also an online communications pioneer, popular blogger, and a sought-after speaker at industry events.

Before establishing MD Becker Partners LLC in 2008, he served as president, chief executive officer, and member of the Board of Directors for several publicly-traded biotechnology companies including commercial-stage Cytogen Corporation (acquired by EUSA Pharma) and development-stage VioQuest Pharmaceuticals, Inc.

While at Cytogen, Mr. Becker held positions of increasing responsibility, including Vice President of Business Development, Industry Relations, Investor Relations and Chief Executive Officer of AxCell Biosciences, a subsidiary of Cytogen focused on signal transduction pathways. During his tenure at Cytogen, Mr. Becker raised in excess of \$130 million in new capital through both public offerings and private placements and in-licensed Caphosol®, a topical oral agent and prescription medical device for the treatment of oral mucositis and xerostomia.

Prior to joining Cytogen, Mr. Becker was with Wayne Hummer Investments LLC, a Chicago-based regional brokerage firm, where he held senior positions as a biotechnology securities analyst, financial advisor and portfolio manager. He was also the founder and Executive Editor of Beck on Biotech, a monthly biotechnology investment newsletter published from July 1998 through March 2001. Mr. Becker was previously with Kidder, Peabody & Co., Gruntal & Co., L.L.C., and Kemper Securities. He has previously held the following financial licenses: Series 7 (Registered Representative), Series 16 (Securities Analyst), Series 63 (Uniform Securities Agent) and Series 65 (Registered Investment Advisor).

Mr. Becker plays an active leadership role as an advocate for the biotechnology industry. He is past Chairman and member of the board of trustees with BioNJ, which is New Jersey's trade association for biotechnology companies, and is currently a member of BioNJ, Pennsylvania Bio, the New Jersey Technology Council (NJTC), and the Pharmaceutical Consulting Consortium, Inc. (PCCI). Mr. Becker placed as a biotechnology/life sciences finalist for the Ernst & Young Entrepreneur of the Year award in both 2004 and 2005 and was listed in BusinessWeek's "CEO's 40 and Under" article in December 2006. He attended DePaul University in Chicago, Illinois.

## JANET L. DALLY

Senior Vice President

Ms. Dally has more than 20-years of experience in the biotechnology, pharmaceutical and medical technology industries as an investor relations advisor, healthcare fund analyst, business development and medical device marketing management, and microbiologist.

Before joining MD Becker, she was President of MontRidge, LLC, a boutique investor relations and strategic consulting firm specializing in the life science industry. She first joined MontRidge as Vice President in 1998. During her tenure at MontRidge, Ms. Dally built meaningful relationships with the executive management of life science clients and the US and European investment community resulting in increased institutional ownership, diversified shareholder base, sell-side analyst coverage, enhanced valuation and successful financing.

Prior to joining MontRidge, Ms. Dally was Vice President of Investor Relations at Burns McClellan, a life sciences communication firm. She also has pharmaceutical industry experience at both Sterling Drug and Forest Laboratories where she held management positions in strategic planning, business development, licensing and M&A.

Ms. Dally has 6-years of experience as an analyst evaluating and recommending biotechnology, pharmaceutical, medical device and healthcare services firms for the Merrill Lynch Healthcare Fund.

She acquired a B.S. in Medical Technology from Rutgers University, M.S. in Microbiology from Wagner College and an M.B.A. from the Tepper School of Business, Carnegie Mellon University.

## JEFFREY MARTINI, PH.D.

Vice President

Dr. Martini joined MD Becker Partners in March 2009 with a diverse background in large pharmaceuticals, biotechnology, academic research, and venture capital.

Prior to joining MD Becker Partners, Dr. Martini worked in the Life Science Investment Group at Ben Franklin Technology Partners (BFTP). BFTP, which is among the most widely known and emulated state technology-based economic development programs, provides capital and expertise to startups, early-stage and established companies. At BFTP, Dr. Martini managed early stage venture capital activities, including the scientific and business-based assessments of numerous biopharmaceutical and medical device start-up opportunities.

Dr. Martini received his Ph.D. in Molecular Pharmacology and Structural Biology from Thomas Jefferson University in Philadelphia, PA and worked as a post-doctoral fellow and graduate student in the Center for Translational Medicine at Jefferson Medical College. While at Jefferson, Dr. Martini was the recipient of numerous awards and research grants including the Jay N. Cohn Investigator of the Year award, the AHA Basic Cardiovascular Science Fellowship, and the American Heart Association Pre-Doctoral Fellowship. Dr. Martini is published in several peer-reviewed journals including PNAS, Nature Medicine, Journal of Clinical Investigation, and Circulation. Dr. Martini graduated from Penn State University with a B.S. in Life Science.

In addition to academic research, Dr. Martini has worked at both Centocor, Inc. and GlaxoSmithKline plc. At Centocor, Dr. Martini was a team leader in process development and while at GlaxoSmithKline, he held positions in biopharmaceutical purification.

## APPENDIX G: LEGAL DISCLAIMER

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